ANNALS OF THE RHEUMATIC DISEASES

EDITORIAL

Among the many advances in medicine and pathology which have marked the twentieth century, the development of systematic research into the pathology and treatment of the chronic rheumatic diseases has been notable. Much credit is due to the pioneer labours and perseverance of the late Dr. Fortescue Fox which led to the awakening of public interest and to important advances in the organization of research through the formation of the Ligue Internationale contre le Rhumatisme in the first instance, and thereafter through the nomination of a British National Committee by the Royal College of Physicians, of which Sir Humphrey Rolleston was the first Chairman. One important result was a national campaign which developed into the Empire Rheumatism Council of which Lord Horder accepted the first chairmanship. He has recently announced his retirement from this position, and the grateful good wishes of all members of the Council will accompany him.

The Council's terms of reference were to stimulate interest in the urgency of the matter among members of the medical profession and the public generally, and to promote research into the causes and treatment of the chronic rheumatic diseases, especially rheumatoid arthritis. At the first meeting of the Royal College of Physicians Committee, a subcommittee on nomenclature had been appointed, and it was decided to publish regular *Reports on the Chronic Rheumatic Diseases*. Four such Reports appeared at annual intervals until the time of the formation of the Empire Rheumatism Council, which then took over the duty of publication and started the journal known as the *Annals of the Rheumatic Diseases*. The present journal first appeared in April, 1940, and two years later the British Medical Association very generously offered to add it to the list of their special Journals, thus enabling it to continue publication throughout the war. At its inception a letter of good wishes and encouragement was received from the Chairman and Secretary of the American Committee for the Control of Rheumatism (Drs R. Pemberton and P. Hench); similar communications came from rheumatologists in many continental countries, and the *Annals* in its present form owes a great deal to their continued interest and help.

In 1950 the Scientific Advisory Committee of the Empire Rheumatism Council, on the initiative of Prof. L. S. P. Davidson, organized an investigation into the aetiological factors associated with rheumatoid arthritis. The work was planned under the direction of the Council's statistician, Dr. E. Lewis-Faning, to ensure that figures and percentages were statistically significant. Questionnaires, completed by experienced observers at nine centres specializing in the treatment of rheumatoid arthritis, seven in England and two in Scotland, were designed to collect information under the following heads:

Aetiological Factors.—Sex incidence; age at onset; psychological precipitatory factors; illness before onset; focal sepsis; familial incidence of arthritis; pregnancy and parturition; menstrual history; home conditions and occupation; climate and season; body type; postural abnormality; peripheral circulation.

Clinical Pattern.—Prodromal symptoms; type of onset (febrile or not, acute or insidious); order and symmetry of joint involvement; radiological appearances; presence of nodules, ganglia, organic diseases, or anaemia; pulse rate; blood pressure; blood sedimentation rate; plasma uric acid levels; loss of weight; illness subsequent to onset.

The total number of patients studied was 532, and a suitable control was sought for each case. The result was a mass of information based on controlled scientific investigation into the various current theories regarding the causation of the disease. This information is of great value to all who have to treat rheumatoid arthritis, and should be studied by all those who write on the subject. Since the Report was too lengthy to be included in a regular issue of the *Annals of the Rheumatic Diseases*, it was published as a Supplement at a very moderate price, but evidently without adequate advertisement, as comparatively few of the regular subscribers to the *Annals* appear to have purchased it. This is unfortunate in view of its value and interest, for the Report may influence research in many ways, and may possibly modify current popular ideas and practice. The Report, which may be obtained from the publishers (The British Medical Association) at a cost of 7*s.* 6*d.* (400 *Fr. frs*, $1.25), should certainly find a place in all Medical Libraries.

COMPARATIVE EFFECTS OF ACTH AND BUTAZOLIDIN IN RHEUMATOID ARTHRITIS

BY

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The administration of 1 : 2-diphenyl-3 : 5-dioxo-4-n-butylpyrazolidine (Butazolidin, Phenylbutazone) to patients with various rheumatic disorders appears to be followed by clinical improvement in a large proportion of cases (Currie, 1951, 1953; Kuzell and others, 1952; Steinbrocker and others, 1952; Stephens and others, 1952; Davies and others, 1952). Although at present the mode of action of this drug remains unknown, it has been claimed to be an "anti-arthritic" and "anti-rheumatic" agent. The meaning of such terms would seem to be obscure in our present state of knowledge. No evidence has been produced that it acts *via* the pituitary-adrenal axis. Suggestions that Butazolidin is a more potent analgesic in rheumatic disease than in other painful conditions are not supported by more than clinical impressions: the assessment of the comparative effects of analgesics is extremely difficult. Steinbrocker and his colleagues (1952), in a blindfold clinical trial, concluded that its analgesic effect was greater than that of salicylates or amidopyrine in rheumatic conditions.

The clinical trials quoted were carried out on relatively large groups of patients and little detailed information is available as to the precise effects of Butazolidin on the various potentially reversible phenomena of rheumatoid arthritis. The present report describes a more detailed study of the effect of this drug on a small group of patients, using for comparison ACTH, a substance whose effect in reversing many of the clinical features of rheumatoid arthritis is well recognized. It would clearly be desirable to compare the effect of simple analgesics such as aspirin in the same manner, but such trials are time-consuming for the patient and this has not so far been possible. The difficulties of measuring the various features of rheumatoid arthritis are great. Clearly, no more than an approximation can be attempted in comparing the effects of two different agents.

Methods

Six patients with active rheumatoid arthritis, considere to have sufficient reversible features to enable therapeutic effects to be measured, were admitted to hospital. After a period of bed rest to allow a reasonably static state to be achieved (at least 2 weeks), they were treated with ACTH and Butazolidin. It was intended, from the long-term point of view, to treat these patients with Butazolidin, but it was felt desirable to compare the effects of ACTH and Butazolidin first, in order to obtain some assessment as to the suitability of Butazolidin for long-term treatment. In three cases ACTH was administered first, and in three cases Butazolidin first.

Dosage.—ACTH was given intramuscularly in divided doses of 100 mg./24 hrs for at least 5 days, the dose then being gradually tapered off to avoid, as far as possible, a rebound relapse. Butazolidin was given orally in doses of 600 to 800 mg./24 hrs for a minimum of 10 days. No other specific treatment was given.

Tests.—Features selected for measurement at regular intervals throughout the trial were as follows:

Erythrocyte sedimentation rate (Westergren),
Urinary output of 17-ketosteroids and glucocorticoids,
Joint swelling and tenderness,
Spontaneous pain,
Power of grip,
Speed of walking.

17-ketosteroids were determined by the standard Zimmerman-Callow method with correction for interfering chromogens (M.R.C. Committee on Clinical Endocrinology, 1951).

Corticosteroids were estimated as formaldehydogenic steroid with β-glucuronidase (Henly, 1952).

Joint swelling was measured by the method of Hart and Clark (1951).

Spontaneous pain and joint tenderness are impossible to measure accurately by ordinary clinical methods, but the amount of pain felt in a number of selected affected joints was roughly graded in three grades (Grade 1—slight, Grade 2—moderate, and Grade 3—severe). A total for a number of joints was thus arrived at.

Joint tenderness was divided into four grades (0—no tenderness, 1—slight tenderness, 2—wincing, 3—wincing

and withdrawal) judged by the response to firm digital pressure on the selected joints.

The grip test was carried out using a sphygmomanometer cuff inflated to 30 mm. Hg.

A second function test was carried out by the timing of a standard walk with a stopwatch.

Range of movement was excluded from this study, in view of the difficulty of obtaining accurate measurements and the absence of adequate relapses between trials.

Times of Testing.—Clinical experience has shown that in the doses used here, ACTH has a rapid effect. It was thought that Butazolidin might have a slower action, and for purposes of comparison, therefore, the response on the fourth to sixth day of ACTH therapy was compared with that on the fifth to tenth day of Butazolidin administration. When more than one assessment was carried out during these periods, the mean of the findings is taken.

Assessment.—Blindfold methods were not used, since one drug was administered by injection and the other by mouth, so that the difficulties of concealment to the patient and the observer alike were out of proportion to the need. With experienced assessors, the need for observer control is diminished; moreover, the assessments took place in a ward when other routine assessments of various drugs were being carried out, and it is doubtful whether the observers were, in fact, directly aware of the exact stage of the trial at any examination.

Placebo effects on the patient cannot be excluded, but with experienced handling these can be minimized, and both drugs had an equal chance of benefiting from such effects. The possibility that the patients were steadily improving throughout the trial, as a result of bed rest independent of the trial substances, must be borne in mind, since this might lead to misinterpretation of the results and to the assumption that both drugs had contributed equally to any improvement in the various criteria selected, whereas, in fact, both had been entirely ineffective.

If full relapse is achieved between each trial this is ruled out, but in practice only partial relapse was achieved in most cases. The degree of relapse is indicated in each analysis, and it will be seen that the amount of improvement during the first trial (independent of the drug used) exceeded the improvement indicated by comparing the assessments before treatment with those during the interval (i.e. relapse period), with the possible exception of the walking time. This trial, moreover, was not designed to establish whether Butazolidin has any effect, but to compare the effect of two different substances. The selection of ACTH for a comparison may be criticized, in view of its variable potency and the variable response of individuals to it (Kellgren and others, 1952). Cortisone was not, however, available, and the response to this is also variable. Whilst the fact that each drug was compared on the same patient does not obviate this difficulty entirely, it does exclude some variables such as the actual reversibility of the pathological changes of rheumatoid arthritis in any one case. Ansell and Bywaters (1952), using somewhat similar methods, have shown that the activity of different batches of ACTH can be roughly assessed by clinical methods of this type. This has also been our experience of batches of ACTH of different potency provided by the Medical Research Council, and the reliability of the assessors in this trial has thus been confirmed.

Clinical Material

Particulars of the six patients with whom these experiments were carried out are shown in Table I.

TABLE I
CLINICAL MATERIAL

Case No.	Sex	Age	Duration of Disease	Erythrocyte Sedimentation Rate mm./hr (Westergren)	Order of Trial
1	F	53	7 yrs	26	ACTH/Butazolidin
2	F	54	1 yr	48	ACTH/Butazolidin
3	M	37	5 mths	36	ACTH/Butazolidin
4	F	28	3½ yrs	97	Butazolidin/ACTH
5	F	51	18 mths	100	Butazolidin/ACTH
6	F	53	6 wks	71	Butazolidin/ACTH

Case 1. Female, aged 53.—A fall in sedimentation rate occurred during ACTH administration from a pre-treatment mean of 26 to 7 mm./hr. Joint swelling was also diminished and there was slight loss of joint tenderness; spontaneous pain did not alter. The erythrocyte sedimentation rate rapidly rose on discontinuation of ACTH, and relapse occurred in 5 days. Joint swelling increased during Butazolidin administration, although spontaneous pain and joint tenderness decreased. There was no improvement in the grip test, but the walking time improved.

Case 2. Female, aged 54.—This patient showed the effect of ACTH on 17-ketosteroid excretion and glucocorticoid excretion. The 17-ketosteroid excretion increased from 9·6 to a maximum of 18·4 mg./24 hrs on the second day of treatment, with a subsequent fall. Glucocorticoid excretion rose from 14·9 and 8·4 mg./24 hrs to 44 mg./24 hrs on the second day, and again fell slowly. There was no similar change when Butazolidin was administered (Table III). The sedimentation rate also fell from 48 to 2 mm. in the first hour on the fifth day of ACTH administration. A fall also occurred during Butazolidin therapy from 28 to 8 mm. in the first hour on the fourth day of treatment. Diminution of joint tenderness and spontaneous pain occurred with both substances, and an improvement in function tests was also seen, but was more marked with ACTH.

Case 3. Male, aged 37.—This patient preferred Butazolidin to ACTH. A greater improvement occurred with Butazolidin in joint tenderness and spontaneous pain, and the grip test also showed more improvement with Butazolidin.

Case 4. Female, aged 28.—This patient again showed the effect of ACTH on 17-ketosteroid and glucocorticoid excretion, with an absence of response to Butazolidin (Table III). The sedimentation rate also was reduced during ACTH therapy, and apparently unaffected by Butazolidin. The loss of pain with the two substances was comparable (Tables V and VI). A steady improvement in walking time occurred with both substances, a greater improvement being observed during Butazolidin administration.

Case 5. Female, aged 51.—This patient responded rather poorly to both trials, except that loss of joint pain and tenderness occurred with both substances. Function tests were irregular, but a greater improvement in walking time was seen with Butazolidin (Table VIII).

Case 6. Female, aged 53.—17-ketosteroid and glucocorticoid excretion were unaffected by Butazolidin, but showed a good response to ACTH (Table III). Loss of joint tenderness was greater with ACTH and spontaneous pain was reduced to a greater extent by Butazolidin. This was the only case in which a reduction in joint swelling was observed during Butazolidin treatment (Table IV).

Results

Erythrocyte Sedimentation Rate (Table II).—The mean erythrocyte sedimentation rate before ACTH treatment was 64 mm./hr (Westergren), and before Butazolidin it was 59 mm./hr (Table II). During ACTH administration it fell to a mean of 35 mm., and during Butazolidin it fell to a mean of 52 mm./hr; the change occurring during ACTH administration is statistically significant ($t=5\cdot373$, $P<0\cdot01$). That occurring during Butazolidin therapy does not reach significance ($t=0\cdot775$, $P>0\cdot05$). This does not, of course, necessarily indicate that Butazolidin has no effect on the erythrocyte sedimentation rate. It indicates that the experiment is sufficiently sensitive in this respect to demonstrate the well-established effect of ACTH on the erythrocyte sedimentation rate in this disease, but offers no evidence that Butazolidin does as has been claimed by Currie (1952). The fall in erythrocyte sedimentation rate associated with this latter drug was much less than that produced by ACTH and within the limits which could occur by chance alone. The mean erythrocyte sedimentation rate during the interval between trials was 2 mm. lower than at the beginning. The mean fall during Butazolidin therapy was only 7 mm., which reinforces the suggestion that Butazolidin itself has no more effect than that which may be produced by rest in bed.

TABLE II

EFFECT OF ACTH AND BUTAZOLIDIN ON ERYTHROCYTE SEDIMENTATION RATE (mm./hr (WESTERGREN))

Case No.	ACTH			Butazolidin		
	Before	During	Change	Before	During	Change
1	26	7	−19	45	30	−15
2	48	2	−46	28	8	−20
3	36	22	−14	14	17	+ 3
4	125	90	−35	97	129	+32
5	84	65	−19	100	90	−10
6	65	26	−39	71	40	−31
Mean	64	35·4	−28·6	59·2	52·3	− 6·9

Mean erythrocyte sedimentation rate before { Trial 1 = 63; Trial 2 = 61

Difference = −2

For ACTH, $t=5\cdot373$; $P<0\cdot01$

For Butazolidin, $t=0\cdot775$; $P>0\cdot05$

17-ketosteroid and Glucocorticoid Excretion.—It was possible to study the 17-ketosteroid excretion in four cases and the glucocorticoid excretion in three cases throughout the trial; the results are shown in Table III. The response was entirely different with the two substances. With ACTH a rise in 17-ketosteroid and glucocorticoid excretion occurred in each case, the glucocorticoid response being the greater. When patients were receiving Butazolidin a fall in 17-ketosteroid excretion occurred, and this was also observed for glucocorticoid excretion in two of the three cases studied. These findings lend support to the belief that Butazolidin does not have a cortisone-like action, and the suggestion of a diminution in 17-ketosteroid and glucocorticoid excretion perhaps deserves further study.

Joint Swelling.—Four cases were suitable for measurement of joint swelling of proximal interphalangeal joints. Several joints were tested in each case and a total numerical reading was obtained. The total ring size during the trial can therefore be

TABLE III

17-KETOSTEROID AND GLUCOCORTICOID EXCRETION

Case No.	17-ketosteroid Excretion (mg./24 hrs)					Glucocorticoid Excretion (mg./24 hrs)				
	Mean of Control Values	Maximum Change				Mean of Control Values	Maximum Change			
		ACTH		Butazolidin			ACTH		Butazolidin	
		Value	±	Value	±		Value	±	Value	±
2	9·6	18·4	+8·8	6·2	−3·4	11·2	44·0	+32·8	6·2	−5·0
4	7·3	14·8	+7·3	4·4	−2·9	11·1	34·1	+23·0	7·0	−4·1
5	4·5	5·4	+0·9	1·1	−3·4	—	—	—	—	—
6	2·7	9·6	+6·9	1·2	−1·5	3·3	39·0	+35·7	5·9	+2·6

compared. Of the four cases, two were treated with ACTH first and two with Butazolidin first. As shown in Table IV, a diminution was observed in every case during the ACTH trial, but during Butazolidin administration an increase in ring size was seen in two of the four cases. These findings should be viewed with caution however, since it is evident from a study of the total ring sizes before ACTH and before Butazolidin therapy that natural variations by this method are considerable and of the same order as the changes found during therapy. Full relapse was not achieved between trials, a mean diminution of 1·5 ring sizes occurring; these findings are therefore inconclusive.

TABLE IV

CHANGE IN TOTAL RING SIZE DURING ADMINISTRATION OF ACTH AND BUTAZOLIDIN

Case No.	ACTH			Butazolidin		
	Before	During	Change	Before	During	Change
1	42	39	−3	39	41	+2
3	41	38	−3	37	38	+1
5	34	32	−2	30	30	0
6	22	19	−3	25	23	−2

Mean ring size before { Trial 1 = 34·5 / Trial 2 = 33 Difference = −1·5

Subjective Changes

(1) *Spontaneous Pain.*—Table V shows the changes that occurred during ACTH and Butazolidin administration; these figures are arbitrary and too much reliance should not be placed on them. They represent no more than an attempt to estimate very roughly the amount of rest pain suffered by an individual patient, so that a comparative assessment of the "total pain" before and during treatment can be made. The "total pain" before each drug was administered was approximately the same, and this does suggest that a consistent estimate can be achieved. The reduction in pain with each substance was of the same order; the change in the figures alone is significant. (For ACTH $t=3\cdot555$, $P<0\cdot05$. For Butazolidin, $t=3\cdot914$, $P<0\cdot05$.) Expressed as a percentage of total pain, ACTH reduced this to 58 per cent. of pre-treatment levels and Butazolidin to 50 per cent. Although only a 75 per cent. relapse was achieved between trials, these findings suggest that the effect of ACTH and Butazolidin on spontaneous pain was of much the same order.

TABLE V

CHANGES IN SPONTANEOUS JOINT PAIN DURING ACTH AND BUTAZOLIDIN ADMINISTRATION

Case No.	ACTH			Butazolidin		
	Before	During	Change	Before	During	Change
1	6	6	0	6·5	5	−1·5
2	6	2	−4	4	3	−1
3	8·5	7	−1·5	8	5·5	−2·5
4	2	0	−2	3	0	−3
5	3	1·5	−1·5	4·5	2	−2·5
6	3	0	−3	7·5	1·5	−6
Mean	4·8	2·8	−2	5·6	2·8	−2·8

Mean spontaneous pain before { Trial 1 = 5·9 / Trial 2 = 4·4 Difference = −1·5

For ACTH, $t=3\cdot555$; $0\cdot01<P<0\cdot05$

For Butazolidin, $t=3\cdot914$; $0\cdot01<P<0\cdot05$

(2) *Joint Tenderness.*—Table VI shows the changes that occurred in joint tenderness during the trial; in both cases a diminution is recorded during treatment of a comparable degree. The "total tenderness" before treatment with either substance is approximately the same, and the change in both cases is significant (for ACTH, $t=4\cdot613$, $P<0\cdot01$; for Butazolidin, $t=4\cdot523$, $P<0\cdot01$). Practically complete relapse (95 per cent.) was achieved in this test; ACTH reduced the joint tenderness to 62 per cent. of pre-treatment levels, and Butazolidin to 57 per cent.

TABLE VI

CHANGES IN JOINT TENDERNESS DURING ACTH AND BUTAZOLIDIN ADMINISTRATION

Case No.	ACTH			Butazolidin		
	Before	During	Change	Before	During	Change
1	5·5	4·5	−1	7·5	4	−3·5
2	10	5	−5	11	3	−8
3	11	8·5	−2·5	11	8	−3
4	4·5	2	−2·5	6	3	−3
5	11	8	−3	13·5	7·5	−6
6	8	2·5	−5·5	10	8	−2
Mean	8·3	5·1	−3·2	9·8	5·6	−4·2

Mean joint tenderness before { Trial 1 = 9·3 / Trial 2 = 8·8 Difference = −0·5

For ACTH, $t=4\cdot613$; $P<0\cdot01$

For Butazolidin, $t=4\cdot523$; $P<0\cdot01$

Function Tests

(1) *Grip Test.*—An analysis of the changes reveals essentially similar results to those found in the study of the subjective phenomena (Table VII). The increase in grip occurring during ACTH therapy does

TABLE VII

EFFECT OF ACTH AND BUTAZOLIDIN ON GRIP TEST (mm. Hg)

Case No.	Power of Grip (mm. Hg)					
	ACTH			Butazolidin		
	Before	During	Change	Before	During	Change
1	70	61	− 9	63	63	0
2	88	185	+97	86	130	+44
3	126	141	+15	111	163	+52
4	180	208	+28	150	177	+27
5	62	66	+ 4	65	70	+ 5
6	64	73	+ 9	46	72	+26
Mean	98·3	122·3	+24	86·8	112·5	+25·7

Mean grip before { Trial 1 = 90·8 / Trial 2 = 94·5 Difference = +3·7

For ACTH, $t=1\cdot555$; $P>0\cdot05$

For Butazolidin, $t=3\cdot058$; $0\cdot01<P<0\cdot05$

not, however, reach a significant level, although that during Butazolidin does. (For ACTH, $t=1\cdot555$, $P>0\cdot05$; for Butazolidin, $t=3\cdot058$, $P<0\cdot05$.) The mean change is much the same for the two substances and virtually complete relapse was achieved between trials (96 per cent.). A mean increase of 24 per cent. in the power of grip during ACTH, and of 30 per cent. during Butazolidin administration occurred.

(2) *Walking Time.*—One case was unsuitable for assessment by this test (Case 3). A constant improvement in walking time occurred during the administration of both substances (Table VIII). It is evident, however, that there was a marked failure to achieve relapse in this test between trials. The mean time before Trial 2 was 4·7 seconds better than before Trial 1 (Table VIII). This figure compares with mean improvements of only 5·5 seconds during Trial 1 and of 5 seconds during Trial 2. It would be unwise, therefore, to draw any comparison between ACTH and Butazolidin in respect of this test.

TABLE VIII

EFFECT OF ACTH AND BUTAZOLIDIN ON WALKING TIME (sec.)

Case No.	Time in Seconds					
	ACTH			Butazolidin		
	Before	During	Change	Before	During	Change
1	9·5	8	−1·5	11·5	8·5	−3
2	28	9	−19	12·5	9	−3·5
3	—	—	—	—	—	—
4	13·5	9	− 4·5	21	13	−8
5	21·5	20	− 1·5	19	14	−5
6	8	7	− 1	13	7·5	−5·5
Mean	16·1	10·6	− 5·5	15·4	10·4	−5

Mean walking time before { Trial 1 = 18·1 / Trial 2 = 13·4 } Difference = −4·7

Mean walking time on { Trial 1 = 10·3 / Trial 2 = 10·7 }

Mean improvement during { Trial 1 = 7·8 / Trial 2 = 2·7 }

Discussion

For purposes of comparison, these tests may be considered in the three groups shown above:

(1) Erythrocyte sedimentation rate, steroid excretion, and joint swelling.
(2) Subjective changes: spontaneous joint pain and tenderness.
(3) Function tests: grip and walking.

(1) The response to the two drugs differs in that: ACTH produces a fall in erythrocyte sedimentation rate, a rise in 17-ketosteroid and glucocorticoid excretion, and a diminution in joint swelling, whereas Butazolidin cannot be shown to have any effect on the erythrocyte sedimentation rate in this experiment; it has either no effect, or a depressing effect, on 17-ketosteroid and glucocorticoid excretion, and no effect on joint swelling.

(2) When subjective effects are assessed (though of necessity in an arbitrary manner), both drugs seem to have roughly the same effect.

(3) Both drugs also appear to have a comparable effect on function tests.

Although there is no evidence as to the effect of analgesics when assessed in this way, it would seem that Butazolidin has no effect which cannot be produced by an analgesic, at least over the short period in which it was administered in this trial. There is no evidence that it has a cortisone-like effect; it is impossible to judge from these tests whether it has an "anti-inflammatory" action, although the lack of evidence of diminution in joint swelling when administered for a short period does not suggest that it has. It must be emphasized that this study was in no way directly concerned with the use of either substance as practical therapy and that these observations were made simply on the short-term effects of the drugs on a few potentially reversible phenomena of rheumatoid arthritis. Nor was this study concerned with the anti-pyretic or toxic effects of either substance. No toxic reactions were, in fact, observed during the trial.

Conclusions

ACTH and Butazolidin have different effects on steroid excretion. No evidence was found that Butazolidin reduces the erythrocyte sedimentation rate when given for a short period, although ACTH given for a shorter period, produced a definite fall. No evidence was found of reduced joint swelling during Butazolidin administration. Pain and function are favourably influenced by both substances to approximately the same degree.

Summary

Six cases of rheumatoid arthritis were studied in detail to observe the comparative effects of ACTH and Butazolidin. There is no evidence that Butazolidin has a cortisone-like effect, but it appears to be roughly comparable to ACTH in its effect on the features of rheumatoid arthritis in which pain is an important element.

I am grateful to Dr. W. S. C. Copeman and to Dr. Oswald Savage for permission to treat their cases, and for their helpful criticism.

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Effets comparés de l'ACTH et de la butazolidine dans l'arthrite rhumatismale

RÉSUMÉ

On étudia minutieusement six cas d'arthrite rhumatismale pour y comparer les effets de l'ACTH et de la butazolidine. On n'a pas pu démontrer que l'effet de la butazolidine soit similaire à celui de la cortisone, mais il semble que cet effet est assez comparable à celui de l'ACTH quand il s'agit de manifestations arthritiques dans lesquelles la douleur constitue un élément important.

Efectos comparados de la ACTH y de la butazolidina en la artritis reumatoide

SUMARIO

Se estudió detalladamente seis casos de artritis reumatoide con el fin de comparar los efectos de la ACTH y de la butazolidina. No hubo pruebas de que el efecto de la butazolidina sea similar al de la cortisona, pero parece que este efecto asemejase bastante al de la ACTH respecto a las manifestaciones artríticas en las cuales el dolor constituye un elemento importante.

OBSERVATIONS ON THE TREATMENT OF RHEUMATOID ARTHRITIS WITH BUTAZOLIDIN

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Introduction

From its introduction into Europe in 1640, cinchona bark (and then quinine) was the only reliable antipyretic drug known until, in 1875, the antipyretic action of salicylic acid was discovered. This was followed by a period of intense actiyity in the examination of the quinine molecule and the synthesis of new febrifuge drugs which would be free from the undesirable side-effects produced by quinine and salicylic acid when administered frequently and in large doses. Although the fashion of strict antipyresis passed, these researches had started the production of a group of the most valuable and frequently employed remedies in the field of practical therapeutics. For convenience, these drugs are grouped together pharmacologically as the "new antipyretics", although they are no longer commonly employed for the purpose which their name implies. It has long been recognized that, apart from their action on fever, all these drugs possessed, in varying degree, the ability to relieve the discomfort and pains associated with many febrile states, and it is as "alleviating remedies" that they are now mainly used.

One of these synthetic drugs was antipyrin (1884) which was formed in an endeavour to produce a synthetic quinine-like substance. As Alstead (1940) commented:

> That the result was such a valuable remedy as antipyrin was, in reality, a lucky chance, for both the conception of the composition of quinine, which served as a type, and the conception of the composition of the antipyrin first obtained were erroneous.

Although the attempt to synthesize quinine had failed, a new ring—pyrazol—had been formed, and this led to the synthesis of yet another compound—amidopyrine.

Amidopyrine, being relatively insoluble, was more slowly absorbed than antipyrin and was found to have a more prolonged, though less powerful, antipyretic action.

As experience with these "new antipyretics" grew, evidence accumulated that they were mild, yet effective, analgesics, and, further, that this analgesic property was most marked in the so-called "rheumatic" and "neuralgic" types of pain. So far as the pain of rheumatic disease was concerned, the salicylates and the pyrazol derivatives were most notably effective. This has been commented upon by many writers (*e.g.* Sollmann, 1917; Cushny, 1910; Poulsson, 1938) since they were first employed. Indeed, the combined antipyretic and analgesic properties were so obvious in the treatment of acute rheumatism that the drugs were regarded as being virtually specific in their action on this disease.

Evidence began to accumulate that amidopyrine was a possible cause of agranulocytosis, and its use, in both Great Britain and America, has become progressively less popular. The salicylates, however, continue to be the sheet-anchor in the drug treatment of acute and sub-acute rheumatic disease, and are believed not only to alleviate the symptoms, but to shorten the course of the disease. The mode of action of the salicylates, however, remains obscure. Recently, attempts have been made to explain this action on the basis of adrenal cortical function (*e.g.* Blanchard and others, 1950; Pfeiffer and others, 1950). Amidopyrine is still extensively employed on the Continent where many physicians regard it as an effective analgesic in rheumatic conditions in which salicylates have failed.

For some years we have been investigating the disproportionately effective analgesic action of these new antipyretics in "rheumatic" diseases, and certain observations appear to us to be satisfactorily established.

(1) Salicylates and amidopyrine are capable of reducing

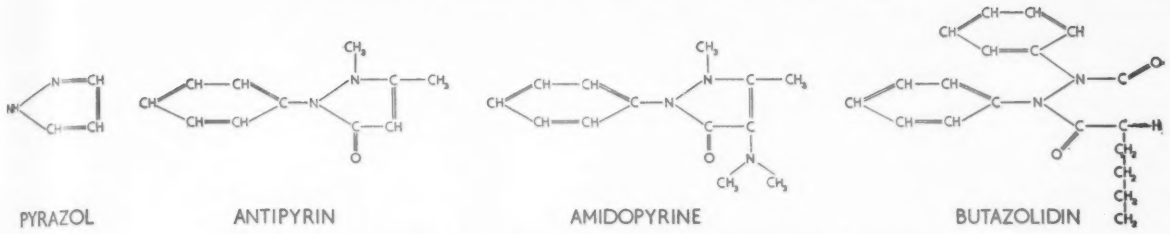

Fig. 1.—Chemical composition of pyrazol, antipyrin, amidopyrine, and Butazolidin

fever and of diminishing joint pain, tenderness, and swelling in acute rheumatic infection.

(2) In rheumatoid arthritis, salicylates are less effective in the control of pain than amidopyrine, but the effect of both drugs is more pronounced than that of the newer and more generally effective anodynes such as pethidine, Physeptone, and Heptalgin.

(3) In some cases of rheumatoid arthritis the administration of antipyrin and amidopyrine is followed not merely by symptomatic relief, but by some reduction in joint swelling and peri-articular oedema and inflammation.

It appeared, therefore, that it might be useful to investigate the effect of pyrazol derivatives on rheumatic disease and not merely as strict antipyretics. The introduction of cortisone provided a yardstick of anti-rheumatic activity and also led most rheumatologists to agree fundamentally on criteria of improvement.

While amidopyrine was being investigated the therapeutic activity of Butazolidin—yet another pyrazol body—was discovered (see Formulae, Fig. 1). Butazolidin was then applied to the treatment of non-articular rheumatism and rheumatoid arthritis (Currie, 1951, 1952).

Since the production of Butazolidin (some 7 months ago) in sufficient quantity to allow of wide application and trial, a number of papers have been published dealing with the drug both clinically and experimentally. We have now applied Butazolidin to the treatment of 424 cases of rheumatoid arthritis, and while so doing, have endeavoured to establish a safe and effective scheme of dosage. This paper is intended to present our findings and to review them in the light of other published work.

Pharmacology

The action of the drug has been studied in two ways:

(1) Work on experimental animals.
(2) Clinical application.

(1) Experimental Work.—Butazolidin is chemically 1·2 diphenyl3·5 dioxo4-n butyl pyrazolidine, and the graphic formula is as previously shown. It differs both in constitution and physico-chemical properties from those pyrazol compounds previously employed in medicine; thus it has the characters of an acid and its sodium salt is easily soluble in water. Pulver (1950a, b) has shown that, unlike amidopyrine, it persists in the blood in high concentrations for 12-24 hrs after administration. The absorption, metabolism, and excretion of the drug have been very fully investigated in animals by Pulver (1950a, b), Pulver and Wilhelmi (1952), Rechenberg and Pulver (1951), Wilhelmi (1949, 1950, 1951, 1952), and Wilhelmi and Domenjoz (1951). It has been shown to possess three main properties (Wilhelmi and Domenjoz, 1951):

(*i*) analgesic;
(*ii*) anti-inflammatory;
(*iii*) antipyretic.

Analgesic.—The effect of the drug on the threshold for electrical stimulation of the dental pulp was tested by Domenjoz and Wilhelmi. The techniques used were those of Koll and Reffert (1938) for dogs, and Gordonoff and Ruckstuhl (1939) for rabbits. These experiments showed that Butazolidin had an analgesic action similar to or less than that of small doses of salicylate, phenacetin, and amidopyrine, but that it did not approach the analgesic effects of morphine.

Anti-Inflammatory.—The anti-inflammatory effects of Butazolidin on the oedema caused by the injection of (*i*) egg albumin, and (*ii*) formalin, into the legs of rats was studied by Domenjoz (1952), Theobald (*cited by* Domenjoz, 1952), and Wilhelmi (1949-52). They showed that the oedema-inhibiting effects of injecting subcutaneously 200 mg./kg. Butazolidin were greater than that of cortisone 2×10 mg./kg., 2×20 mg./kg., and 2×50 mg./kg., or of ACTH 4×2 mg./kg. This action of Butazolidin was also demonstrated (Wilhelmi, *cited by* Domenjoz, 1952) in experimental inflammation produced by other methods, thus:

Ultra violet light dermatitis in rats.
Mustard oil chemosis in rabbits.
Arthritis in immunized rabbits after intra-articular injection of antigen.

Domenjoz (1952) has demonstrated diminished capillary permeability to colloidal dyes after Butazolidin administration, and marked anti-histaminic effects in the perfused rabbit ear and in the guinea-pig. It seems

possible that these effects contribute to the anti-inflammatory effects of the drug.

Antipyretic.—The antipyretic action of the drug has been demonstrated by Wilhelmi and Domenjoz (1951) in yeast fever in rats and in *B. coli* pyrexia in rabbits.

(2) Clinical Application.—The most marked therapeutic effect of the drug in cases of rheumatoid arthritis is relief of pain. With the doses we employ, almost all patients experience relief within 2 or 3 days of beginning treatment. Synchronously there is lessening of stiffness in affected joints and performance improves. We have already emphasized that these effects may all be part of the analgesic action. After 7 to 10 days' treatment a reduction in joint swelling can be demonstrated in a proportion of cases; this appears to be most noticeable in early and acute cases. It is possible that the differing percentages of patients showing reduction in joint swelling reported by *e.g.* Kuzell (1952), Kuzell and others (1952), Stephens and others (1952), Steinbrocker and others (1952a, b), and ourselves (Currie, 1951; Brown and Currie, 1952), depends upon the number of early or acute cases in the groups treated. The erythrocyte sedimentation rate and plasma viscosity are reduced in some patients, particularly in early and acute cases. This feature is much more marked, however, in the treatment of acute rheumatic fever, in which disease also the antipyretic effect is striking (Fleming and Will, 1953).

Apart, however, from these particular effects, it appears, as Kuzell and his colleagues also comment, that the drug has some general anti-rheumatic effect. In the case of rheumatoid arthritis the effect of the drug appears to be to suppress the activity of the disease, while in rheumatic fever the whole course of the disease appears to be greatly shortened. It has been alleged (*B.M.J.*, 1952a), that all the effects reported or confirmed in cases of rheumatoid arthritis could be explained on the basis of the analgesic action of the drug. This appears to be unlikely, for drugs known to be much more powerful analgesics than Butazolidin (*e.g.* Physeptone, Heptalgin, pethidine) fail to produce anything like similar relief.

In addition to its effects on rheumatic conditions, however, Butazolidin has been shown to have a number of other therapeutic applications. Thus Kuzell (1952) is of opinion that its most striking application is in acute gout and chronic gouty arthritis. Engleman and others (1952) claim that the blood uric acid is markedly diminished after Butazolidin administration, although there is "no striking uricosuria". Steinbrocker states that many conditions respond to Butazolidin administration, and mentions two cases of peri-arteritis nodosa, which had previously responded only to ACTH, and were controlled by Butazolidin. Similarly, Kling (1952) alleged that his best results were obtained in eight cases of spondylitis ankylopoietica which had failed to respond to *x*-ray therapy and cortisone; six showed great improvement in a few days, and the erythrocyte sedimentation rate fell from 45 to 25 mm./hr.

Studies of the blood Butazolidin content after intravenous, intramuscular, and oral administration led us to the following conclusions:

(*i*) The drug is rapidly and almost completely absorbed from the alimentary tract.

(*ii*) Absorption after intramuscular injection is irregular; we believe that there may be some precipitation of the drug at the site of injection in some cases.

(*iii*) Oral administration is the method of choice, not only because of its ease and simplicity, but also because of the regular and adequate absorption which follows its employment.

Considerable variation appears to occur in the rate at which Butazolidin is removed from the blood (in the patients studied, from 15 to 45 per cent. per day; 75 per cent. showed a value of between 20 and 25 per cent. per day).

We have found that for suppression of symptoms in rheumatoid arthritis a blood concentration of 8-11 mg. per cent. appears to be required. This is effected in a majority of cases by an initial dose of 800 mg. in the first 24 hrs, and can be maintained with subsequent doses of 200 mg. daily (Figs 2 and 3, opposite).

Davies and others (1952) pointed out that no advantage appears to be gained by raising the daily dose above 1·0 g., and with this we agree. But, further continued high dosage does not, in our experience, result in continued increase of the concentration of Butazolidin in the blood, and we have found that the blood level becomes fixed at 12·5-15·5 mg. per cent. (Fig. 4, opposite). The drug does not exhibit cumulative features in patients, and this is in accord with Pulver's findings in experimental animals. Our investigations have also indicated that, although an initial blood level of 8-11 mg. per cent. is required to suppress symptoms, remission can be maintained by considerably lower concentrations of 4·6 to 8·0 mg. per cent. We have found, too, that initiation and maintenance of clinical improvement, and relapses, follow closely the pattern of the level of the drug in the blood. It would thus appear that the varying requirements of different patients in respect of maintenance doses is related to the rate at which they metabolize the drug. Because of this variation in the rate of Butazolidin metabolism in different patients we have evolved the following dosage

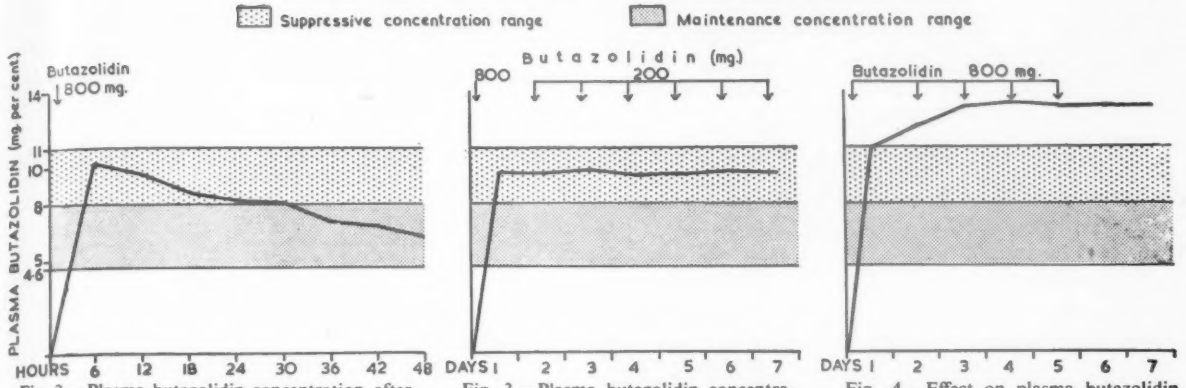

Fig. 2.—Plasma butazolidin concentration after a single dose of 800 mg.

Fig. 3.—Plasma butazolidin concentration in a patient treated according to our dosage schedule

Fig. 4.—Effect on plasma butazolidin of repeated large doses (800 mg. daily)

schedule which meets the requirements of almost all cases (Table I).

TABLE I
DOSAGE SCHEDULE

Day	No. of Doses	Amount (mg.)
First	4	200
Second	3	200
Third	3	200
Fourth	2	200
Fifth	2	200
Sixth	1	200

If, by the fourth day of treatment, there is no subjective improvement, we estimate the blood Butazolidin level. If this is found to be within the "suppressive" level, we discontinue the drug as evoking no response. If, however, the blood level is inadequate for suppression of symptoms, we either increase the dose or give the drug by intramuscular injection. The latter alternative is indispensable where the keratin-coated pills are passed by the patient in the stools. Should symptomatic relapse occur on a maintenance dose of 200 mg. daily, the dose is increased to 200 mg. twice daily. If higher doses are required for maintenance, the blood level of the drug is estimated. If the patient remains improved on 200 mg. daily, the frequency of the dose is diminished to every other day.

Results

The results of treatment by Butazolidin in 424 cases of rheumatoid arthritis are set out in Table II.

TABLE II
ANALYSIS OF RESULTS

No. of Patients	Subjective Improvement	Improved Performance	Objective Improvement
81 (previously reported)	77	77	24
343	327	319	105
424	404 (95 per cent.)	396 (93 per cent.)	129 (30 per cent.)

The diagnostic criteria used were these:

(1) Acceptable clinical history.
(2) Polyarthritis.
(3) Radiological confirmation or lack of evidence of other joint disease.
(4) Normal blood uric acid.
(5) Negative Wassermann and Kahn reactions.
(6) Negative Widal test for abortus fever.
(7) Negative gonococcal complement-fixation test.
(8) Raised erythrocyte sedimentation rate and/or raised plasma viscosity.

The criteria of improvement are set out in Table III.

TABLE III
CRITERIA OF IMPROVEMENT

Subjective or Symptomatic	Objective
Pain and tenderness	Joint measurements
Performance	Reduced erythrocyte sedimentation rate and plasma viscosity
Well being	Appearance of joints

The erythrocyte sedimentation rate was ascertained repeatedly in 42 patients; in four it fell within the first 10 days of treatment, and in a further eight cases within one month of beginning treatment.

The results again illustrate the subjective nature of performance tests.

In the patients treated in this series, symptomatic improvement, when once established, was invariably maintained so long as the drug was continued.

Many of these patients have been on the small maintenance doses we have described for 6 months, seven for 11 months, and two for 12 and 13 months respectively. Improvement in performance has been seen to continue steadily in some patients even on very small doses.

Toxicity.—In the series of cases here reported, the incidence of toxic side-effects has been notably low (4·7 per cent.), and those that occurred were mild in nature (Table IV). Of the 424 patients treated, twenty showed side-effects during treatment, and in only three did treatment have to be stopped.

Other reports of Butazolidin therapy have given a varying incidence of toxic effects from 0-100 per cent. (Table V).

The heading "Miscellaneous", in Table V, includes thrombocytopenia, anaemia, leucopenia, purpura, epistaxis, haematuria, euphoria, insomnia, dyspnoea, vertigo, palpitation, "substernal pressure", stomatitis, "blisters of mouth", "intertriginous lesions", auricular fibrillation, fever, jaundice, "swelling of face", and injection abscess.

Besides these toxic effects, three deaths have been attributed to the drug, one from haematemesis and

TABLE IV

INCIDENCE OF TOXIC SIDE-EFFECTS

Nature of Reaction	No. of Cases	Comment
Oedema	4	Disappeared in two cases despite continued treatment, and in the other two only when the drug was withdrawn
Albuminuria	3	All cleared despite continued treatment
Skin rash	4	Possible alternative causes in three (phenobarbitone, enema, and shellfish respectively); drug readministered to these without reappearance of rash. Fourth patient also sensitive to morphine, codein, and iodoform
Nausea	6	Drug continued in all
Stomatitis	1	No granulopenia. Drug re-administered without recurrence of stomatitis
Tachycardia	1	Transient, drug continued
Tingling of toes	1	Transient, drug continued

TABLE V

TOXIC SIDE EFFECTS REPORTED BY OTHER AUTHORS

Author	Date	No. of Cases	Toxic Reactions						
			Total	Nausea Vomiting Dyspepsia	Oedema	Haema-temesis or Melaena	Agranulo-cytosis	Skin Rash	Miscel-laneous
Bach	1952	50	4	2	—	—	—	—	2
Bourne	1953	not stated	5	—	1	—	—	—	4
Crowther and Elgood	1952	"small series"	"frequent"				1		
Davies and others	1952	100	16	25 only 2 severe	8			3	3
Gillhespy	1952	15	1	—	—	—	—	1	—
Granirer	1952	20	20	—	6	2	—	4	8
Hart and Johnson	1952 a and b	16+60	14	2	3	—	—	6	—
Hogarth	1952	not stated	not stated	—	—	—	—	—	—
Jarvis	1952	not stated	1	—	—	—	1	—	—
Kelly	1952	not stated	"few"	not stated					
Kersley and others	1952	14	"no gross oedema occurred"						
*Kuzell and others	1952	140	47	24 some very mild	17	—	—	6	5
Loxton and others	1952	50	11		3		1	5	2
Shulman	1952	237	3	—	2	—	—	"a few mild"	1
Slot	1952	4	0	—	—	—	—	—	—
†Steinbrocker and others	1952b	52	13	4	3	—	—	3	9
Stephens and others	1952	188	83	9	9	2	—	9	54
Tait	1952	not stated	not stated	—	—	—	1	—	—

* Error in addition from paper quoted.
† Some patients showed two toxic features; tabulated under both.

two from agranulocytosis (*B.M.J.*, 1952b; *Lancet*, 1953).

In considering these reported toxic effects, three points must be borne in mind:

(1) Not all symptoms occurring during drug therapy are necessarily due to the drug.

(2) The evidence incriminating Butazolidin in many reports may be described as being, at best, presumptive.

(3) The toxicity of any drug must be weighed against the benefits conferred by it. At the worst, Butazolidin compares very favourably with orthodox chrysotherapy in this respect.

We attribute the low incidence of toxic side-effects in our own group of patients firstly to careful dosage, and secondly to careful selection of patients, avoiding the aged and all suspected of having a poor cardiac reserve. With regard to two reported toxic features (dyspepsia and agranulocytosis), we would offer the following observations. Nausea, anorexia, abdominal discomfort, and vomiting have not been seen since we began to use enteric-coated tablets. The fact that Butazolidin is, like amidopyrine, a pyrazol derivative may have led to the anticipation of similar blood changes to those ascribed to amidopyrine. We have already drawn attention to the very different rates of absorption, metabolism, and excretion of the two substances as well as their physico-chemical dissimilarity, and it would therefore appear probable that their toxicity may also be different. Indeed, von Rechenberg has administered Butazolidin, in gradually increasing doses, to three patients who had recovered from amidopyrine agranulocytosis. The patients were known to respond with a rapidly developing granulocytopenia to minute doses of amidopyrine, but all tolerated full doses of Butazolidin without alteration in the number or type of the circulating leucocytes.

Conclusions

(1) Butazolidin administration affords rapid and substantial relief to a large proportion of patients suffering from rheumatoid arthritis.

(2) In many cases there is, in addition, an apparent suppression of the activity of the disease.

(3) Almost all cases relapse slowly on withdrawal of the drug.

(4) With careful dosage and selection and management of patients, the drug appears to be remarkably free from serious toxic properties.

Summary

The preliminary work leading to the therapeutic trial of Butazolidin is described.

The literature dealing with the drug experimentally and clinically is reviewed.

The results of treatment in 424 cases of rheumatoid arthritis are presented.

A plea is made for careful selection of cases and moderation in doses.

We wish to thank Dr. J. C. Eaton for carrying out the estimations of plasma Butazolidin content (by his own modification of Pulver's method), and Dr. J. W. Macfarlane for again, so willingly, placing beds at our disposal.

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Remarques sur le traitement de l'arthrite rhumatismale par la butazolidine

RÉSUMÉ

On décrit le travail préliminaire de l'essai thérapeutique de la butazolidine.

On passe en revue la littérature sur l'aspect clinique et expérimental de ce médicament.

On présente les résultats du traitement dans 424 cas d'arthrite rhumatismale.

On préconise un triage soigneux des malades et une posologie modérée.

Observaciones sobre el tratamiento de la artritis reumatoide con butazolidina

SUMARIO

Se describe el trabajo preliminar del ensayo terapéutico de la butazolidina.

Se pasa en revista la literatura sobre el aspecto experimental y clínico de este producto.

Se presenta los resultados del tratamiento en 424 casos de artritis reumatoide.

Se aboga la selección cuidadosa de los casos y la moderación posológica.

TREATMENT OF ACUTE RHEUMATISM WITH BUTAZOLIDIN

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A favourable experience of Butazolidin in the treatment of rheumatoid arthritis and the experimental reports that it appears to influence the resolution of inflammatory exudates, suggested that it might be of use in treating acute rheumatism.

Case Reports

(1) Female, aged 17, had been treated for rheumatic fever 3 years ago, but it appeared to have been a mild attack, and she had been well since; 6 days before admission she had developed pain, stiffness, and swelling of both ankles, and the knees, hands, and shoulders also became involved; 3 days later she had sternal and interscapular pain with cough, and complained also of anorexia, headache, profuse perspiration, and occasional vomiting. The joint pains responded to some extent to salicylate.

Examination.—On admission (temperature 101·2° F., pulse 110, respirations 25), she complained of severe sternal pain and was dyspnoeic and cyanosed. There was no notable swelling of the joints, but the knees were tender. The heart sounds were regular, very soft, and a systolic murmur was present at the apex. A soft to-and-fro friction rub was heard at the base. The erythrocyte sedimentation rate was 94 mm./hr (Westergren). On the 9th day of illness an area of bronchial breathing was noted at the left base and pericardial friction persisted. Her condition deteriorated, and three days later the fever increased with rapid pulse (130) and respirations (40).

Progress.—Two days later she developed a circinate erythema over the abdomen, buttocks, and backs of the thighs, and there was a recurrence of severe joint pains with increase in praecordial pain. She was now very dyspnoeic and cyanosed, and coarse pericardial friction was heard and felt over the whole praecordium. Streptomycin ½ g. twice daily was added on the 15th day of illness, but there was no response and she deteriorated rapidly to a moribund condition on the 22nd day of illness.

Therapy.—All other treatment was discontinued and she was given three tablets Butazolidin daily (Fig. 1). The next morning there was a remarkable improvement; she was comfortable, and asked for food, and the tempera-

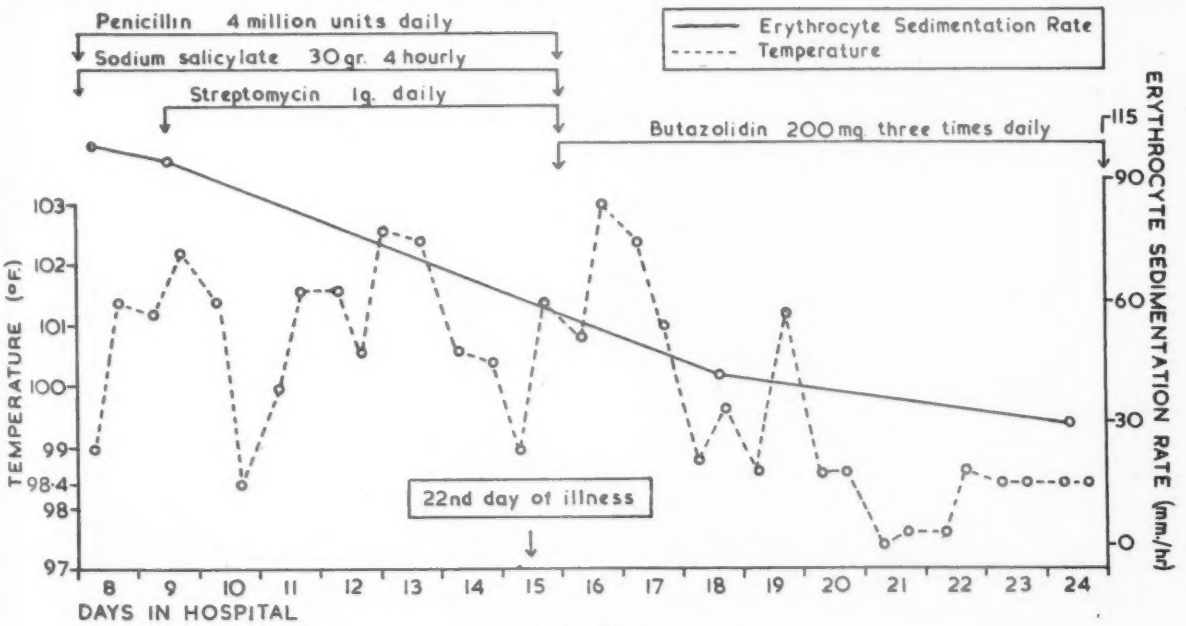

Fig. 1.—Case 1.

ture fell to normal levels in 24 hours. Two days later the pericardial friction had completely gone and has not recurred, and a week later the erythrocyte sedimentation rate was 38 mm./hr. There was a gradual improvement in the quality of the heart sounds, and the first sound, which had been obscured by a soft murmur, was clearly audible and pure by the 40th day.

A favourable convalescence with a continued fall in the erythrocyte sedimentation rate suggests that she is likely to make a complete recovery.

(2) Schoolboy, aged 11, had developed a cold, with cough and spit, but no sore throat, 12 days before admission. A week later he fell and thought he had hurt his right ankle. An *x* ray was negative, but 2 days later he still had pain in the left ankle and also in the wrist. He was now fevered and complained of severe headache.

Examination.—On admission (temperature 104° F., pulse 120, respirations 30), he was complaining bitterly of pain in the right and left legs. The right ankle and most of the leg was very swollen, red, and tender, and the left ankle and wrists were affected to a lesser extent.

Therapy.—The pain responded to salicylate, but fever continued, the right leg remained acutely inflamed, and the erythrocyte sedimentation rate continued to rise to 128 mm./hr. The salicylate was now discontinued and he was given Butazolidin, 200 mg. three times daily. During the next 24 hrs the temperature settled, and remained normal. The joints improved rapidly and were normal in appearance 4 days later, and the patient was now completely comfortable. Three days later the erythrocyte sedimentation rate was 95 mm./hr, and a soft murmur, which had been noted at the apex during the earlier stages, could not be detected. He has continued to make a favourable convalescence.

(3) Schoolboy, aged 9, had a severe sore throat 5 weeks before admission; it improved in the next few days, and he seemed well until 10 days later when he had pain in the knees and ankles. There was some response to aspirin, but he continued to have low fever and a high erythrocyte sedimentation rate. In the fifth week an apical systolic murmur was heard.

Examination.—On admission there was only a little joint stiffness, but the erythrocyte sedimentation rate was 95 mm./hr, and low fever continued. The first apical sound was partially replaced by a soft murmur, and the pulmonic sound was loudly accentuated.

Therapy.—There was no improvement during treatment with aspirin and penicillin, and 4 weeks after admission Butazolidin, 200 mg. three times daily, was substituted. During the next few days the temperature fell to normal levels and the erythrocyte sedimentation rate slowly improved. The cardiac murmur was unchanged.

(4) Schoolgirl, aged 15, had had two previous attacks of acute rheumatic fever, which had responded to salicylate therapy, but resulted in a mitral stenosis, which, until the present illness, had caused no symptoms; 3 weeks before admission she developed for the third time acute rheumatic fever with severe joint swelling, pain, and tenderness in both knees, ankles, elbows, and shoulder. During the next 10 days the pain and tenderness responded to 15 gr. aspirin four times daily, but the temperature remained around 101·5° F.

Examination.—On admission (temperature 101·6° F.) she looked ill, and there was swelling and acute tenderness of the knees, ankles, and right elbow.

Therapy.—She was treated with Butazolidin, 200 mg. thrice daily, and there was a notable response of the temperature and joint swelling (Fig. 2). After 5 days the

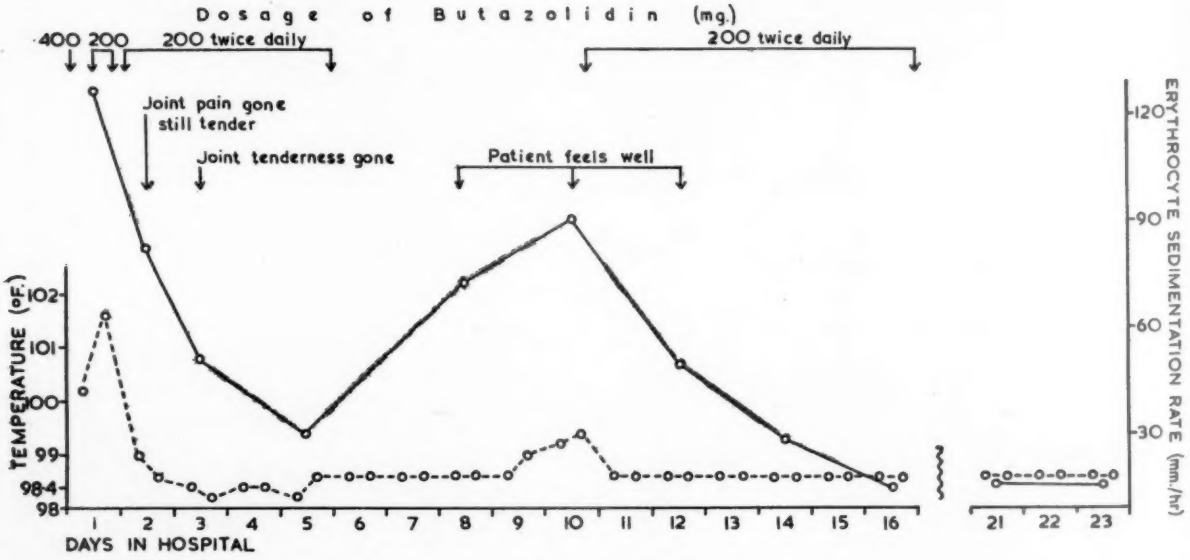

Fig. 2.—Case 4.

drug was withdrawn and the patient continued to feel well till the 9th day, when there was a rise of temperature and erythrocyte sedimentation rate. Butazolidin in the same dose produced an immediate similar response; on the 16th day the drug was discontinued, and there has been no relapse. There is no evidence of further cardiovascular damage.

(5) **Schoolboy, aged 12,** with no previous history of rheumatic disease, 14 days before admission complained of sore throat, which cleared up after 3 days' treatment with sulphonamide. A week before admission he developed acute pain and stiffness in the right knee, which became red and swollen, and was followed by the left elbow and right wrist. There was high fever (102·5° to 103·5° F.), and no response to 15 gr. aspirin four times daily.

Examination.—On admission (temperature 103·2° F.), he was very ill, with severe inflammation and tenderness of the left elbow, wrist, and right knee.

Therapy.—Both fever and joint pains responded to Butazolidin, 200 mg. twice daily. Butazolidin was stopped on the 13th day and he has continued to make a favourable convalescence. There is no evidence of cardiac involvement.

These unexpectedly favourable results raise the hope that further experience will establish Butazolidin as a useful drug in the treatment of acute rheumatic diseases. The present treatment with sodium salicylate is unsatisfactory, both because of the unpredictable results, and because of the huge doses required. In these cases, a small dose of Butazolidin, consisting of one or two tablets daily, was sufficient to produce a response. In our experience with similar doses in many cases of chronic rheumatism, toxic reactions are infrequent and of small significance.

Summary

The use of Butazolidin is reported in five cases of acute rheumatism, which showed little or no response to salicylates.

In each case there was a rapid improvement in joint pain, temperature, and erythrocyte sedimentation rate, and the patient made a good recovery.

There were no toxic reactions. Relapse on withdrawal of Butazolidin, which occurred in one case, was quickly checked by a few additional doses.

We are indebted to Dr. J. P. Currie, Glasgow Royal Infirmary, for details of Cases 4 and 5.

Traitement du rhumatisme articulaire aigu par la butazolidine

RÉSUMÉ

On relate l'emploi de la butazolidine dans cinq cas de rhumatisme articulaire aigu totalement ou partiellement réfractaire aux salicylates.

Dans tous les cas on nota une amélioration rapide de la douleur articulaire, de la température et de la sédimentation globulaire et le rétablissement des malades.

Il n'y eut pas de réactions toxiques. Une rechute qui survint dans un cas après la suppression de la butazolidine, fut rapidement enrayée par quelques doses additionnelles.

Tratamiento del reumatismo poliarticular agudo con butazolidina

SUMARIO

Se relata el empleo de la butazolidina en cinco casos de reumatismo poliarticular agudo, totalmente o parcialmente refractario a los salicilatos.

En todos los casos se notó una mejoría rápida del dolor articular, de la temperatura y de la sedimentación eritrocitaria y los enfermos recobraron la salud.

No hubo reacciones tóxicas. Al discontinuar la butazolidina hubo una recaída, rapidamente reprimida con pocas dosis adicionales.

A RHEUMATOID SYNDROME OCCURRING IN THE ELDERLY

BY

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The classification and nomenclature of disease is an arbitrary procedure depending on the maximum number of constant symptoms and signs falling together frequently enough to form a recognizable pattern. The pursuit of the classical manifestations of any disease often blinds clinicians to numerous atypical but related forms. This paper presents a syndrome probably allied to rheumatoid arthritis but not generally recognized.

It occurs in middle aged and elderly people, presenting essentially as a pyrexia of unknown origin. There is initial general malaise, and loss of appetite and weight, with an intermittent pyrexia reaching at times to 103° F. or higher. With these symptoms there is a vague generalized ache confined most often to the shoulders and cervical region, but sometimes involving the rest of the spine and back, chest, abdomen, and limbs. Movements of the affected joints are performed with difficulty, but the movements are full and the limitation is usually due to discomfort. There is no swelling or redness of the joints. The chest pains may be sharp or aching but are rarely pleuritic. There may be episodes of diarrhoea and vomiting, conjunctivitis, and erythematous rashes.

A profound constitutional disturbance is shown by the persistent fever, anaemia, and loss of weight. Examination may reveal some lymph-node enlargement with or without splenomegaly. Usually, however, on clinical examination, nothing abnormal can be found apart from the fever, tachycardia, and occasional tenderness to pressure over the painful areas.

Special investigations show the blood sedimentation rate to be extremely high, usually well over 100 mm./hr, and often reaching 130 mm./hr. This is a most characteristic finding. The haemoglobin falls because of a secondary iron-resistant anaemia. The white blood count may be raised with a polymorphonuclear leucocytosis often associated with a lymphocytosis. Türck cells may appear in the peripheral blood, or there may be a mild eosinophilia. In severe cases leucopenia develops. The blood albumin/globulin ratio is altered, with a fall in the albumin and an occasional rise in the globulin. Sometimes there is a reversal of the ratio. The blood fibrinogen is invariably raised, often to figures as high as 900 mg. per cent. The bone marrow rarely shows any significant or characteristic abnormality, but there may be an increase in plasma cells to the upper limits of normal, some of the forms being atypical.

Chest *x* rays may show vague transient shadows and opacities, and the skeletal system some degree of de-calcification. Blood cultures and agglutinations are negative. In typical cases of the syndrome the joints show no radiological change, but cases have been included with osteo-arthritic change, and these form transitional types towards true rheumatoid arthritis. The ultimate prognosis is good, but the disease may run a long course of months or years.

Case Reports

Case 1. A 62-year-old farmer was admitted to the Radcliffe Infirmary on May 19, 1944, under Professor L. J. Witts. He had not felt really well since a total dental extraction 6 years previously. In August, 1943, he had noticed that he was losing energy, feeling cold and shivery, and on occasions sweating profusely. In November he had been admitted to a nursing home with an intermittent fever and an erythrocyte sedimentation rate of 143 mm./hr (Westergren). Agglutinations to Salmonella and Brucella organisms as well as blood culture had been negative. At that time he developed mild stiffness and discomfort around the neck and shoulders for the first time. *X* ray of the cervical spine showed minor osteo-arthritic changes. In December he developed "rheumatic" pains in his hands. By March, 1944, he had improved considerably, but on admission his previous symptoms were exacerbated, and he had vomited six times.

He had been a farmer in Australia between 1910-1916 but had had to leave the country because of attacks of dysentery. He had been well up to the time of his tooth extractions, but from time to time had had attacks of conjunctivitis.

Examination.—He was very thin. Temperature 99·6° F.; pulse 108; respiration 20; blood pressure 110/65. There was limitation of movement of the cervical spine, but all other joint movements were good. Moderate axillary lymph node enlargement. Spleen not palpable. Other systems natural.

Erythrocyte sedimentation rate 61 mm./hr (Wintrobe).
White blood count 3,000, 42 per cent. polymorphs, haematocrit 32 per cent., colour index 0·97, blood plasma uric acid 1·73 mg. per cent.
Total plasma proteins, 7·2 g. per cent., albumin 2·7 g. per cent., globulin 4·1 g. per cent., fibrinogen 719 mg. per cent.
Takata Ara strongly positive.
X ray of cervical spine showed new bone formation between atlas and occiput, but no evidence of ankylosing spondylitis.
Sternal puncture showed a poorly cellular marrow with a small proportion of cells resembling myeloma cells.

It was considered that he had myelomatosis. Throughout his stay in hospital he ran a low grade fever which did not respond to any therapy.

Therapy.—He was discharged after transfusion of one pint of blood.

Later Developments.—On June 23, 1944, he was re-admitted for repetition of the tests, and was found to have improved. The backache was less severe and had moved to the lumbar region. Sternal puncture did not confirm a diagnosis of myelomatosis. Bone *x* rays revealed no abnormality. The albumin/globulin ratio remained reversed.

In November, 1945, he was re-admitted with fever, backache, and a dry cough. There was now slight limitation of wrist extension and shoulder movement, but no gross changes could be observed.

Erythrocyte sedimentation rate 75 mm./hr (Westergren).
Haemoglobin 66 per cent.
Albumin/globulin ratio reversed.
Fibrinogen 1,003 mg. per cent. There was a trace of albumin in the urine but no Bence Jones protein.
X ray of the chest revealed a small round opacity at the left base of undetermined nature.

He continued to run a fever up to 102·8° F. and a tachycardia between 100-120. He received a transfusion of two pints of blood and was discharged unimproved, but at home he once again felt better.

On March 15, 1950, at the age of 68 he was re-admitted under the care of Dr. A. M. Cooke for the fourth time, complaining of similar indefinite symptoms. He had signs of chronic bronchitis in his chest.

Erythrocyte sedimentation rate 130 mm./hr (Westergren).
Haemoglobin 70 per cent.
White blood count 3,200 with neutropenia and a proportion of Türck cells.
Wassermann reaction negative.
Agglutinations to Salmonella, Brucella, and Leptospira organisms negative.
Albumin/globulin ratio remained reversed.
Electrocardiogram showed a sinus tachycardia of 110.
Urine contained protein and granular and cellular casts.

Salicylates, chloramphenicol, and aureomycin had no effect on the fever which rose to 102° F. Chest *x* ray showed a diffuse increase in lung markings suggesting infiltration rather than congestion since there was no increase in heart size. *X* rays of the hands revealed mild decalcification only. On April 15, 1950, he was discharged home unchanged.

Once more he improved, and when last heard of was well, apart from osteo-arthritis of the spine. His disease had persisted with remissions for 12 years.

Case 2. A 57-year-old housewife was admitted to the Radcliffe Infirmary on February 6, 1952, under Dr. F. G. Hobson. She complained of a generalized diffuse ache in her back, shoulders, and chest for the previous 5 years. The symptoms had gradually developed after partial thyroidectomy for nodular goitre. This had not been toxic. For the year before admission she had had attacks of fever and sweating and had lost 4 stone in weight. She had paraesthesiae in her arms, vague abdominal discomfort with flatulence, and before admission an attack of vomiting and diarrhoea for which no cause could be found. On one occasion she had had an erythematous rash over her shoulders. For the previous few months she had had a dry cough.

Examination.—She looked reasonably well. Temperature 98·6° F.; pulse 100; blood pressure 120/75. There was discomfort in the cervical region on rotating the neck, but all movements were full and other joints were natural. There was tenderness over the eighth and ninth ribs antero-laterally. Liver edge just palpable. Tongue red and smooth. Short apical systolic murmur. Other systems natural.

Erythrocyte sedimentation rate 113 mm./hr (Westergren).
Haemoglobin 83 per cent.
White blood count 7,300.
Total plasma proteins 6·3 g. per cent., albumin 3·2 g. per cent., globulin 2·2 g. per cent., fibrinogen 857 mg. per cent.
Marrow puncture normal.
Urine normal.
Chest *x* ray showed well-healed infiltration of apices and a small opacity at the left apex whose nature was not determined.
Barium meal and cholecystogram normal.
Agglutinations to Salmonella and Brucella organisms negative.
Blood culture grew *Streptococcus faecalis*, probably a contaminant.

After 6 weeks the fever gradually settled and the erythrocyte sedimentation rate fell to 65 mm./hr.

Therapy.—A pneumoperitoneum had been induced in case there should be pus under the diaphragm, but this only revealed a spleen double the normal size on screening. No treatment had any effect on the course of her illness. She improved and gained weight and lost her aches and pains. When seen in out-patients on May 2, 1952, she was much better but had pains below her sternum and over the left ilium. Haemoglobin 82 per cent., erythrocyte sedimentation rate 69 mm./hr (Westergren). Repeated sputum examination revealed no tubercle bacilli. The duration of her illness had been over 5 years.

The Figure shows her temperature, pulse rate, and erythrocyte sedimentation rate during her stay in hospital.

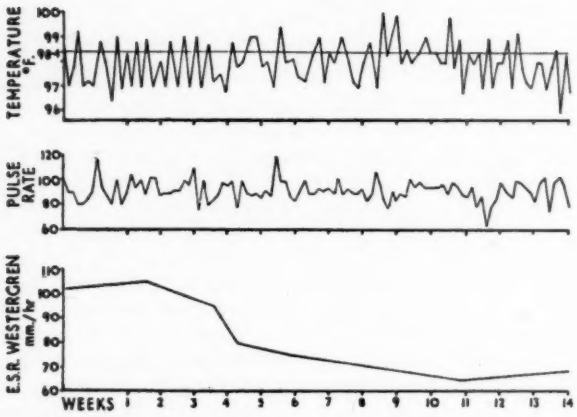

FIGURE.—Case 2. Temperature, pulse, and sedimentation rate.

Case 3. A 73-year-old gardener was admitted to the Radcliffe Infirmary under Dr. F. G. Hobson on February 2, 1951, with 6 weeks' history of headaches, cough, loss of weight, and pallor. He was found to have mild heart failure, liver enlargement, ankle oedema, and signs of broncho-pneumonia. The chest infection responded well to streptomycin and the oedema subsided with rest in bed, but he continued to run a fever up to 100° F.

Erythrocyte sedimentation rate 112 mm./hr (Westergren).
Haemoglobin 80 per cent.
White blood count 12,000.
Total plasma proteins 5·7 g. per cent., albumin 3·0 g. per cent., globulin and fibrinogen 2·7 g. per cent.
Thymol turbidity and colloidal gold tests negative.
Wassermann reaction negative.
Sternal puncture revealed normal marrow with 5·6 per cent. plasma cells.

The anaemia was resistant to iron and the haemoglobin fell to 63 per cent. He was discharged, and when seen in out-patients a month later was complaining of stiffness in the hands, wrists, back, hips, and knees. Externally there was no obvious abnormality or limitation of movement. *X* ray of the left hand showed mild decalcification with osteo-arthritic changes in some of the joints. Erythrocyte sedimentation rate 112 mm./hr (Westergren). Physiotherapy gave no relief. On his last visit hi erythrocyte sedimentation rate was 104 mm./hr (We gren), and he was having persistent pain in the backs of both thighs. He had been unwell for 2 years.

Case 4. A 62-year-old widow was admitted to the Radcliffe Infirmary under Professor L. J. Witts on July 12, 1941, complaining of vague aches in the shoulders, arms, neck, and lumbar region for the previous year. She felt weak and short of breath and had lost 4-5 stone over this period.

Examination.—She was pale and thin.

Temperature 100° F.; pulse 120; blood pressure 140/80. There was a harsh apical systolic murmur and scattered rhonchi in her chest. Cervical lymph nodes slightly enlarged. Spleen not palpable. Other systems normal.

Erythrocyte sedimentation rate 67 mm./hr (Westergren).
Haemoglobin 40 per cent.
White blood count 7,800, 72 per cent. neutrophils, 21 per cent. lymphocytes, 5 per cent. monocytes, haematocrit 26 per cent.
Marrow puncture revealed a few atypical plasma cells.
Small quantities of occult blood found in stools.
Gastroscopy showed atrophic mucosa with a haemorrhagic patch.

She ran a low grade fever throughout her stay in hospital. She was discharged but had to be re-admitted because of exacerbation of symptoms. The ache in the shoulders, back, and hips had increased, and there was limitation of movement due to pain.

Erythrocyte sedimentation rate 148 mm./hr (Westergren).
Haemoglobin 40 per cent.

In view of the presence of occult blood it was thought that she might have an abdominal neoplasm. Sigmoidoscopy revealed only an ulcerated pile and a laparotomy performed by Mr. Elliot-Smith showed no abnormality. A skin biopsy taken at this time was normal. *X* ray of her right shoulder showed marked osteo-arthritis. After the operation her aches gradually returned and she continued to run a fever with tachycardia. She was discharged unimproved and undiagnosed.

She had been unwell for nearly 2 years.

Case 5. A 58-year-old medical practitioner was seen by Dr. A. M. Cooke in August, 1943, on account of lassitude and generalized aches and pains, chiefly in the limbs, which had come on over the previous year. The pains were in the muscles rather than the bones.

Erythrocyte sedimentation rate 28 mm./hr (Westergren).
Haemoglobin 80 per cent.
Blood pressure 120/80.
X ray of the spine showed a crack in C 6, perhaps due to a recent fall, and some osteo-arthritis. Physical examination revealed no abnormality.

He continued to feel ill and lost 3 stone over 5 years.

Professor A. W. M. Ellis saw him a few months later complaining of flatulence and indigestion.

A barium meal showed no lesion.
Erythrocyte sedimentation rate 110 mm./hr (Westergren).
Haemoglobin 75 per cent.
White blood count 9,000, eosinophils 720.

He had had bouts of fever and sweating. The pains were now chiefly in the deltoids and lumbar region. Periodic examinations revealed no obvious abnormality. A cholecystogram was normal. Urine contained occasional traces of albumin. He gradually improved after a while, and by March, 1945, was much better. When last seen in September, 1951, he looked and felt well, although he had occasional twinges of pain.

His illness had lasted 3 years.

Case 6. A 64-year-old widow was admitted to the Radcliffe Infirmary on April 16, 1952, under Dr. F. G. Hobson. For 7 weeks she had had pains in the backs of both thighs, cervical spine, and shoulders. She had felt generally unwell with fever and sweating and had lost weight. There had been no joint swelling. Massage, codeine, penicillin, and salicylates had no effect and she had become worse.

Examination.—She was thin and pale. Temperature 99° F.; pulse 88; blood pressure 150/90. There was considerable wasting of both thighs and triceps, but the joints were normal and allowed full range of movement. She was tender over the hamstring muscles. No nodules could be found. Slight cervical lymph node enlargement and thyroid a little full. Apart from a slight kyphosis other systems were normal.

Erythrocyte sedimentation rate 100 mm./hr (Westergren).
Haemoglobin 86 per cent.
White blood count 6,050.
Total plasma proteins 7·3 g. per cent., albumin 3·9 g. per cent., globulin 2·6 g. per cent., fibrinogen 621 mg. per cent.

After a few days salicylates seemed to control the fever, which rose when they were discontinued. The second time they were tried it took 9 days for the fever to settle. The muscle pains improved, but she continued to lose weight. At no time was there a pronounced tachycardia.

Chest *x* ray was clear and *x* rays of the hands and knees were normal.
Urine natural.
By June 5, 1952, the erythrocyte sedimentation rate had fallen to 52 mm./hr (Westergren), and the temperature had settled to 99° F.
Agglutinations to Salmonella and Brucella organisms negative.

After 2 months in hospital she was discharged, gaining weight and symptomless.

Case 7. A 68-year-old statistical worker was admitted to the Radcliffe Infirmary under Dr. A. M. Cooke on August 9, 1943. For 7 weeks he had suffered from night sweats and severe vertical headaches on the right and left sides. For about the same period he had experienced severe lumbar backache and for 4 weeks a weakness of both legs when attempting to walk. This was a soreness rather than pain. Over this period he had vomited several times and had been constipated. Many years previously he had had jaundice, cervical adenitis, and peritonitis following appendicectomy. There was no family history of rheumatism.

Examination.—He was very thin. Temperature 99·2° F.; pulse 74; respiration 20; blood pressure 125/75. There was no abnormality of the cardiovascular, respiratory or alimentary systems. There was a generalized stiffness of both legs, but the reflexes were normal.

Erythrocyte sedimentation rate 107 mm./hr (Westergren).
Haemoglobin 70 per cent.
White blood count 16,000, neutrophils 11,680, eosinophils 160, lymphocytes 3,360, monocytes 800.
Lumbar puncture and C.S.F. normal.
Chest *x* ray showed a raised right diaphragm with adhesions at both bases.
Skull *x* ray, spine *x* ray, barium meal, barium enema, and intravenous pyelogram normal.
Wassermann reaction negative.
Blood urea 30 mg. per cent. Total plasma proteins 7·0 g. per cent., albumin 4·4 g. per cent., globulin and fibrinogen 2·6 g. per cent. Plasma uric acid 2·1 mg. per cent.
Occult blood present in very small amounts.

During his stay in hospital he ran a slight pyrexia with the pulse rate between 70 and 90. He gained weight and improved. On August 31, 1943, he was discharged much improved. At follow-up on November 22, 1944, he was complaining of rheumatic pains in the buttocks and thighs, which on examination were wasted. There was no evidence of temporal arteritis, and the erythrocyte sedimentation rate was 28 mm./hr (Westergren).

Discussion

The syndrome here described resembles the prodromal stage of rheumatoid arthritis before the joint lesions have become established. The other collagen diseases may also present with similar prodromal symptoms, but in typical cases the pattern of the disease quickly becomes established.

Atypical manifestations of rheumatoid arthritis were stressed by Ropes and Bauer (1945); Ellman and Ball (1948) described three cases of rheumatoid disease with joint, lung, and heart involvement; Bywaters (1949) described a variant of rheumatoid arthritis resembling palindromic rheumatism; Littler (1951) studied a remarkable case with Felty's and Sjögren's syndrome associated with signs of mitral stenosis not due to rheumatic fever; *post-mortem* studies by Baggenstoss and Rosenberg (1943) revealed the generalized nature of rheumatoid arthritis with visceral involvement; Leichtentritt (1943)

showed the lesion in peripheral nerves; the characteristic tendon changes were described by Kellgren and Ball (1950).

As Duff (1948) has pointed out, the characteristic change in all diseases of the collagen system is fibrinoid change followed by connective tissue proliferation. The degree of each varies according to the disease. In rheumatic fever and rheumatoid arthritis the fibrinoid necrosis is overshadowed by a proliferative and inflammatory response; in disseminated lupus erythematosus the fibrinoid change predominates; in periarteritis nodosa the adventitia of the small vessels proliferates while the fibrinoid change is reserved for the media and intima; in scleroderma the proliferation of collagen is so overwhelming that it is only with difficulty that patches of fibrinoid change can be found in the walls of small vessels. Although these diseases are usually clear entities, atypical forms have been described in which features of several may be present together (Banks, 1941). Similarly, Bevans (1945) described two cases of scleroderma with "wireloop" kidney lesions similar to those found in disseminated lupus erythematosus.

To add to the difficulties of diagnosis, disseminated lupus erythematosus may present without cutaneous manifestations (Rakov and Taylor, 1942). Rheumatoid arthritis and rheumatic fever resemble each other more than they do the other collagen diseases in that they show the characteristic rheumatoid nodule. Intermediate types may occur however. Rosenberg and others (1943) found sixteen cases of heart lesions indistinguishable from rheumatic heart disease in thirty *post-mortem* examinations of patients with rheumatoid arthritis. Furthermore, Friedberg and Gross (1934) described four cases of rheumatic fever with lesions typical of periarteritis nodosa. These similarities and differences have been discussed by Dawson and Tyson (1936).

Kellgren (1952) suggested that in rheumatoid disease there is a breaking up of the collagen-polysaccharide connective tissue complex, the collagen disintegrating into peptides which diffuse out and promote an inflammatory response. Menkin (1947) has similarly postulated the breakdown of protein to peptides which initiate the normal inflammatory response and has fractionated these. The tissue which remains after the collagen disintegration is rich in polysaccharides and produces fibrinoid change by replacing the damaged tissue. That connective tissue change may occur at the molecular level without microscopic evidence is suggested by the case of a boy who died of scleroderma but whose tissues showed no histological change (MacCallum, 1926).

These atypical forms are stressed because they reveal the confusing clinical and pathological picture which the collagen diseases may present, the typical symptoms appearing to mimic each other.

The syndrome here described approximates more closely to rheumatoid arthritis than to the other collagen diseases on account of the long course, muscle wasting, fever, anaemia, good prognosis, and joint involvement which occurs in transitional types. This, however, was rarely gross either clinically or radiologically except in Case 1. The most characteristic feature of the syndrome is the diffuse ache round the shoulders and cervical region, at times involving also the back, chest, and limbs. In those cases without joint involvement it must be postulated that there is a generalized alteration in the connective tissue, and where the change occurs in fascial planes or muscles there is pain and discomfort. If there is peripheral nerve involvement there may be paraesthesia. Albuminuria may result from the non-specific glomerulo-nephritis so frequently found by Baggenstoss and Rosenberg (1943). Four of the cases had flatulence and abdominal discomfort. Three had spells of diarrhoea and vomiting for no apparent cause. It is perhaps significant that, in the thirty *post-mortem* examinations of Rosenberg and others (1943), two patients had died of prolonged diarrhoea of undetermined aetiology.

The transient opacities in the chest seen in the radiographs may have been due to involvement of the lungs by the rheumatic process; it was clinically manifest by an unproductive cough.

In no case was there any evidence of ankylosing spondylitis and the significance of the osteo-arthritic changes was difficult to interpret in view of the age of the patients.

The lupus erythematosus test of Haserick (1945) was attempted in Case 2 with negative results. There was no evidence of lupus erythematosus cells in the four cases where a marrow puncture was done, but atypical plasma cells were seen twice and the count was a high normal once. The significance of this is obscure, but in general plasma cells proliferate in association with a rise in the globulin (Barr, 1950). In the cases reported, there was no gross alteration in the globulin except in Case 1, but the albumin was low except in Case 7. The high blood fibrinogen probably accounted for the raised sedimentation rate.

In no case was there any evidence of mitral stenosis. The illness may last for several years with remissions, but the ultimate prognosis is good. Salicylates were only partially effective in Case 6, in the others they had no effect at all.

The term "rheumatoid" disease should be more extensively used to describe this and similar syn-

TABLE

Case No.		1	2	3	4	5	6	7
Age and sex		62 ♂	57 ♀	73 ♂	62 ♀	58 ♂	64 ♀	68 ♂
Pain in	Shoulder girdle	++	++	++	++	+	++	—
	Cervical spine	++	++	++	++	+	++	—
	Lumbar spine	++	+	+	+	+	—	+
	Other joints	Wrists	—	Hands, wrists, hips, knees	Hips	—	—	—
	Muscle	—	Arms	Arms, thighs	Arms	Arms, thighs	Thighs	Thighs, buttocks
	Chest	—	+	—	+	+	—	—
	Abdomen	Flatulence	Flatulence	Flatulence	Pain in right iliac fossa	Flatulence	—	—
Joint swelling		—	—	Right wrist	—	—	—	—
Weight loss		++	++	++	++	++	++	++
Fever and sweating		++	++	++	++	++	++	++
Dry cough		+	+	+	—	—	—	—
Rash or conjunctivitis		+	+	—	—	—	—	—
Lymph node enlargement		+	+	—	+	—	+	—
Splenomegaly		—	+	—	—	—	—	—
Vomiting and diarrhoea		+	++	+	—	—	—	Vomiting
Erythrocyte sedimentation rate (highest)		145	105	112	148	118	100	107
Haemoglobin (lowest) (per cent.)		50	78	63	40	70	81	70
White blood cells		Türck cells Leucopenia	Leucocytosis	Leucocytosis	Normal	Eosinophilia Leucocytosis	Leucocytosis	Leucocytosis
Bone marrow		Atypical plasma cells	Normal	5·6 per cent. plasma cells	Atypical plasma cells	—	—	—
Albumin/Globulin ratio		2·2 : 4·6	3·3 : 2·6	3·0 : 2·7	—	—	3·9 : 2·6	4·4 : 2·6
Fibrinogen		1,003	831	—	—	—	778	—
Urine		Casts, Protein	Normal	Normal	Normal	Protein	Normal	Normal
X ray	Chest	Vague shadows	Vague shadows	Normal	Normal	Normal	Normal	Basal adhesions
	Joint	Cervical osteo-arthritis	Normal	Osteo-arthritis left hand, mild decalcification	Osteo-arthritis right shoulder	Osteo-arthritis cervical spine	Normal	Normal
Duration with Remissions (years)		12	5 +	2 +	2	3	2 months +	1 +

dromes. Some of the periodic fevers described by Reimann (1951) may well be examples of a similar disease process. So far no *post-mortem* studies of this syndrome have been available and a skin biopsy from Case 2 revealed no abnormality. All the cases described were undiagnosed and discharged as pyrexias of unknown origin. Perhaps if this syndrome is recognized it will save numerous unnecessary investigations being performed on repeated admissions in an effort to reach a simple diagnosis.

The accompanying Table summarizes the main findings.

Addendum

After I had submitted this paper for publication, my attention was drawn to a communication by Kersley (1951) on a related myalgic syndrome of acute onset and crippling severity. Thirteen patients, of average age 71, had widespread pain and tenderness of muscles, and a high blood sedimentation rate; three of them developed slight swellings in the hands or knees. Muscle biopsies on four patients were normal. Three patients treated with ACTH or cortisone responded well, but in others the condition tended to become chronic. In several cases the syndrome

followed stress; it appears to fit in well between the syndrome described above and true rheumatoid arthritis.

Summary

A syndrome is described affecting elderly people and characterized by generalized aching, especially of the shoulders and cervical region, but often also involving the back, chest, and limbs. There is a prolonged intermittent fever with sweating and great loss of weight. The sedimentation rate is very high and there is a secondary anaemia. The joints need not be involved. The course may be prolonged over months or years, but the ultimate prognosis is good.

The syndrome is more closely related to rheumatoid arthritis than to the other collagen diseases. It is suggested that the term rheumatoid disease be more extensively used to describe this and similar syndromes.

I should like to thank Professor L. J. Witts, Dr. F. G. Hobson, and Dr. A. M. Cooke for permission to publish details of the cases which were under their care. I should also like to thank them and Mr. J. R. P. O'Brien for helpful criticism, and the Biochemistry and Pathological Departments for those investigations which were not carried out by myself.

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Syndrome rhumatoide survenant chez des vieillards

RÉSUMÉ

On décrit un syndrome atteignant les vieillards et caractérisé par une douleur généralisée, surtout accentuée aux épaules et dans la région cervicale mais s'étendant souvent au dos, à la poitrine et aux extrémités. On note une fièvre intermittente et prolongée, avec des sueurs et un amaigrissement marqué. La sédimentation globulaire est très rapide et il y a une anémie secondaire. L'atteinte articulaire n'est pas de règle. La maladie peut évoluer pendant des mois et des années, mais le pronostic ultérieur est bon.

Ce syndrome est plus étroitement lié à l'arthrite rhumatismale qu'aux autres maladies collagènes. On suggère l'emploi plus fréquent du terme "maladie rhumatoide" pour désigner ce genre de syndromes.

Síndrome reumatoide ocurriendo en los ancianos

SUMARIO

Se describe un síndrome que ocurre en los ancianos y que se caracteriza por un dolor generalizado, particularmente de la espalda y de la región cervical, extendiéndose a menudo al dorso, al pecho y a las extremidades. Se nota una fiebre intermitente y prolongada, con sudores y un adelgazamiento pronunciado. La sedimentación globular es muy rápida y hay anemia secundaria. No hay necesariamente implicación articular. La enfermedad puede prolongarse durante meses o años, pero el pronóstico ulterior es bueno.

Este síndrome está más estrechamente relacionado con la artritis reumatoide que con las demás enfermedades colágenas. Se sugiere el empleo más extendido del término "enfermedad reumatoide" para describir este síndrome y otros del tipo similar.

HISTOCHEMICAL STUDIES OF RHEUMATIC CONDITIONS

I. OBSERVATIONS ON THE FINE STRUCTURES OF THE MATRIX OF NORMAL BONE AND CARTILAGE

BY

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Recently, specific enzymes have become available in highly purified form, which will attack the two main constituents of the ground substance of connective tissue.

Collagenase (from *Cl. Welchii* filtrates, purified by the method of Bidwell and van Heyningen, 1948), attacks collagen but has a negligible action on other proteins.

Hyaluronidase (Benger) acts upon the mucopolysaccharide components, not only those built up from hyaluronic acid as the repeating unit, but also upon chondrin, where the repeating unit is chondroitin sulphuric acid.

Trypsin, on the other hand, will digest the majority of normal proteins, but will not attack collagen unless this has been denatured by some form of pre-treatment, *e.g.* by heat or by 20 per cent. urea solution.

The use of these enzymes for the differential removal of the ground substance components from histological sections, followed by specific staining methods for these components to see the extent to which they have been attacked by their enzymes, should provide a convenient method of investigating the chemical nature of rheumatic changes. But, before undertaking a study of rheumatoid material, it is necessary to apply the method to normal tissues: firstly, in order to obtain results which can be used as a set of controls, and secondly for purposes of standardizing the technique.

The present communication deals with the results obtained from normal bone and cartilage.

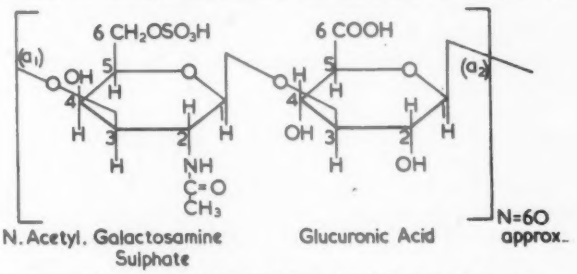
Methods

Material.—The articular cartilage of apparently normal human knee joints obtained at autopsy was used. Sections of the whole thickness of the cartilage and the underlying articular lamella were used, either cut frozen without fixation or decalcification, or fixed in 70 per cent. ethanol and decalcified before paraffin embedding in 1 per cent. hydrochloric acid in 70 per cent. ethanol. After this collagenase will still work, though at a reduced speed, whereas formalin fixation inhibits it more or less completely.

In these sections there is a zone of each kind of tissue, collagen with almost no chondrin in the superficial fifth of the cartilage, collagen and chondrin in the next three-fifths, collagen, chondrin, and calcium in the basal fifth, and collagen and calcium phosphate in the strip of lamellar bone below this.

Staining.—The presence of the chondrin was followed by metachromatic staining with toluidine blue, 0·02 per cent. at *p*H 3·5, and the less highly polymerized polysaccharide by staining with the periodic acid-Schiff method. The distribution of the two kinds of polysaccharide is quite distinct, though both are sometimes present together.

The relation between the chemical structure of the chondrin and its staining reactions is based on the original observations of Lison (1936) and Michaelis (1947) on metachromatic staining with toluidine blue and similar dyes, and on the use of periodic acid to oxidize adjacent glycol groups (Hotchkiss, 1948). Michaelis, on physicochemical grounds, relates metachromatic staining to polymerization of the dye molecules, but, with less evidence, relates this in turn to polymerization of the substrate. Lison merely regarded the metachromasia as evidence of the presence of sulphuric esters of high molecular weight. Now, it is known from analysis that the primary alcohol group on carbon-6 of the galactosamine is always sulphated in chondrin (Formula 1).



Formula 1.—Chondroitin-Sulphuric Acid (Meyer, Odier, and Sigrist, 1948).

Changes in metachromasia must therefore be related to alteration in the freedom of this sulphate group.

The formula recently given by Meyer, Odier, and Siegrist (1948) for chondroitin-sulphuric acid (Formula 1) leaves only the ends of the molecular aggregates available for periodic acid-Schiff oxidation which requires the presence of two adjacent glycol (-CHOH-) groups. These investigators give the molecule as a straight chain polysaccharide, consisting of approximately 60 units of a repeating disaccharide composed of N acetyl.-galactosamine and glucuronic acid, joined throughout by a 1 : 3 linkage. As the requisite molecular structure can only occur at the end of these molecules, they should stain but weakly with the P.A.S. method. Breakdown in molecular size increases the number of such end-groups, so that an increase in the intensity of the P.A.S. staining reaction should result. Formula 2, depicting the repeating disaccharide, shows how such groups arise by hydrolysis of the links attaching it to the adjacent units (A_1 and A_2 are the reacting groups). The actual mechanism of the P.A.S. reaction consists in the oxidation by periodic acid of two adjacent glycol groups to give two aldehyde groups (Formula 3), which then react with Schiff's reagent to give a red colour. An alternative formula, put forward earlier by Bray, Gregory, and Stacey (1944) and by Haworth (1947), gives the repeating unit as a branching trisaccharide containing an additional molecule of glucuronic acid joined to the first by a 1 : 2 linkage (Formula 4). Here, too, the same principle would hold.

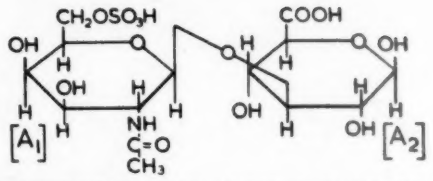
Direct observations of the toluidine blue and P.A.S. methods of staining show that their results are commonly reciprocal. The hyaline cartilage of the foetus is intensely metachromatic with toluidine blue, but quite negative to P.A.S., and the areas of adult cartilage staining most metachromatically with the former, also show the weakest reaction with P.A.S.* The specificity of staining with P.A.S. is, however, so wide that positive reactions require more careful interpretations than negative ones. It merely implies the presence of a double glycol grouping without giving information as to the rest of the molecule, and it is conceivable that these might arise in the material under treatment otherwise than by the polysaccharide breakdown shown in the above formulae.

Pre-treatment with "Hyalase" would break the polysaccharide chains *completely* to their constituent units, which are sufficiently small and soluble to diffuse away, so that subsequent P.A.S. staining would give a negative result. This is borne out by experience.

The presence of calcium was determined by alizarin or Von Kossa's technique, which always corresponded. Collagen was stained by Van Gieson's method.

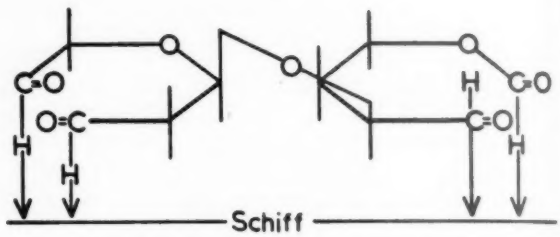
Decalcified sections were obtained by the use of O.1.N. hydrochloric acid on the cut sections for 5 minutes at room temperature. In these the calcium was completely removed but it is unlikely that any significant hydrolysis of the protein or polysaccharide would have occurred. Alternatively, prolonged exposure of tissues in bulk was carried out before embedding in paraffin using 1 per cent. HCl in 70 per cent. ethyl alcohol.

* There are local exceptions to this.

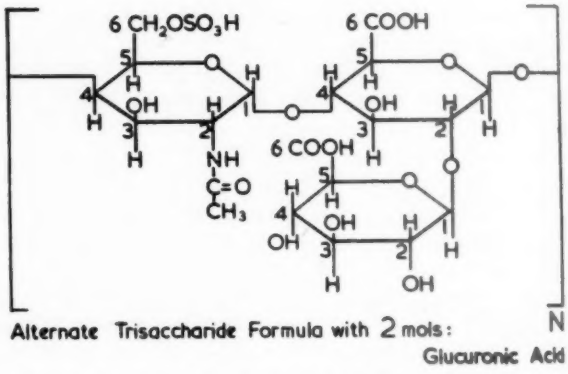


DISACCHARIDE UNIT. Hydrolysis of 1:3 links at a_1 and a_2 in Formula 1 has produced adjacent glycol groups at A_1 and A_2 in Formula 2. Oxidation of these with periodic acid converts them to aldehydes which give a red colour with Schiff's reagent.

Formula 2.—Chondroitin-Sulphuric Acid.



Formula 3.—Chondroitin-Sulphuric Acid.



Formula 4.—Chondroitin-Sulphuric Acid (Bray, Gregory, and Stacey (1944); Haworth, (1947)).

Enzyme Treatment.—The sections were incubated loose in pots of the enzyme solutions and subsequently transferred to normal saline prior to staining and mounting on slides. Where more than one enzyme treatment was applied, they were washed by floating in saline prior to transferring to the next enzyme solution.

The enzyme preparations employed were:

(*i*) *Hyaluronidase.*—Benger's "Hyalase" at a concentration of 2,000 "Benger Units" in 25 ml. saline for 20 hours at 37° C. which allows for slight variations of potency in individual 1,000-unit batches of the material. The enzyme acts only on fresh material.

(*ii*) *Collagenase.*—The material (supplied by Messrs. Burroughs and Wellcome) consisted of the K-toxin of

TABLE

TRYPSIN AND COLLAGENASE SPECIFICITY TESTS

Two Substrates placed in two Sets of four Test Tubes each and treated with 10 ml. of four Solutions (incubation 2 hrs at 37° C.).

Enzyme	Substrate	Result	Solution			
			Phosphate Buffer (*p*H 8)	0·5 per cent. Trypsin in Phosphate Buffer	Borate Buffer (*p*H 7·4)	Collagenase (1 mg./ml.) in Borate Buffer
Trypsin ..	100 mg. dry powdered fibrin	Macroscopic	No change	Cloudy, approximately half dissolved	No change	No change
		Non-protein N (mg.)	0·14	1·33	0·14	0·14
Collagenase ..	10 ml. concentrated collagen suspension	Macroscopic	No change, opaque	No change, opaque	No change, opaque	Water-clear, only few coarse strands left
		Non-protein N (mg.)	2·06	2·06	2·06	3·70

Cl. Welchii, purified by the method of Bidwell and Van Heyningen (1948) and put up as a freeze-dried powder. Its strength was 13·3 Q units per mg. (71 Q units per mg. N). Only traces of α-toxin, hyaluronidase, or desoxyribonuclease were stated to be present. It was readily soluble in Palitch's borax/borate buffer *p*H 7·4 in which it is stable. The concentration used was 1 mg. dry powder/ml. buffer. The incubation time was usually 24 hours at 37° C.

(*iii*) *Trypsin* (L. Light and Co. Ltd.).—This was a purified preparation of trypsin in powder form, stated to be free from contamination by other enzymes. The strength used was 0·5 per cent. solution of powdered enzyme in phosphate buffer at *p*H 8. Incubation was for one hour at 37° C.

Tests for Enzyme Specificity.—It is necessary to show that collagenase will digest collagen but not other proteins, and conversely that trypsin will digest non-collagenous protein but not collagen. For the non-collagenous protein substrate, fibrin was chosen, as this protein was likely to be encountered later in pathological material. 100-mg. portions of dry, powdered fibrin were weighed out into four test tubes. To show collagenase activity, a collagen suspension, made from rat-tail tendons by the method of Nageotte and Guyon (1931), was used. By decanting off the supernatant fluid at intervals, the collagen was concentrated until a white, completely opaque suspension was obtained. The substrate consisted of 10 ml. of this collagen suspension. A second series of four tubes were put up.

10-ml. portions of the two enzyme solutions used for the histological work, and 10-ml. portions of their respective buffer solutions as controls, were added to the two sets of four tubes which were then incubated for 2 hrs at 37° C.

Enzyme activity was then assessed, both macroscopically and also by precipitating undigested protein with Somogyi's reagents and then estimating the non-protein-nitrogen (MicroKjeldahl) in the filtrates from these. The results are set out in the Table.

The results show the two enzymes to be satisfactory for the purpose in view. Trypsin will readily digest fibrin but will not attack collagen, whereas collagenase digests collagen but appears inactive against fibrin.

Additional Tests

(*a*) *Trypsin.*—Commercial preparations, which are usually made by glycerol extraction of pancreas, contain considerable amounts of both lipase and amylase. Heavy contamination with these might digest any lipoid or glycogen present in the sections and affect the histological picture. To test for lipase, the substrate used was 3 ml. alkaline litmus-milk, any change of colour from blue towards pink being observed, while 3 ml. 1 per cent. starch solution was used as substrate for amylase. Starch hydrolysis was tested for with Benedict's solution and also with iodine for residual starch.

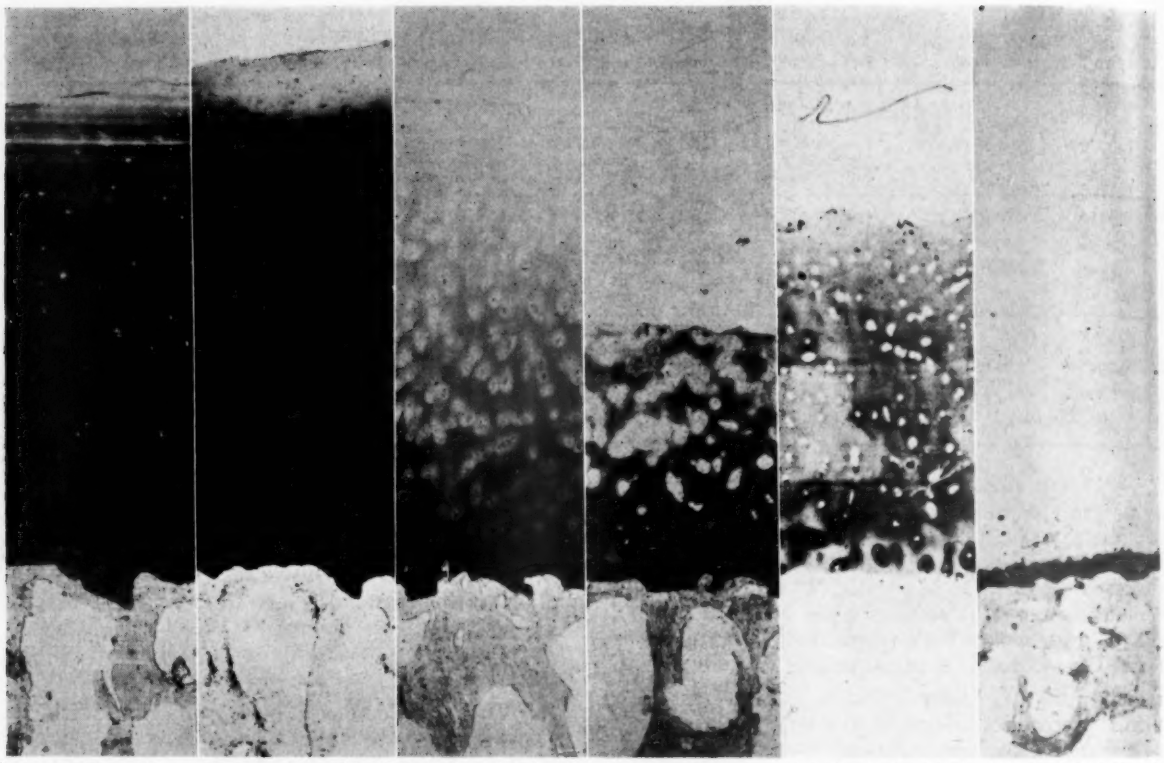
Control tubes using boiled enzyme were put up and a commercial trypsin preparation was tested similarly for comparison. Incubation was for 1 hr at 37° C.

No amylase and only a slight trace of lipase could be detected in our preparation whereas the commercial preparation was strongly positive for both.

(*b*) *Hyaluronidase.*—Naked-eye observation of tests carried out with collagen suspension and fibrin sufficed to show the "Hyalase" preparation to be inactive against these substrates. Pilot trials carried out on sections and followed by toluidine blue or P.A.S. staining had shown it to be active against the mucopolysaccharides present, and capable of bringing about their complete removal.

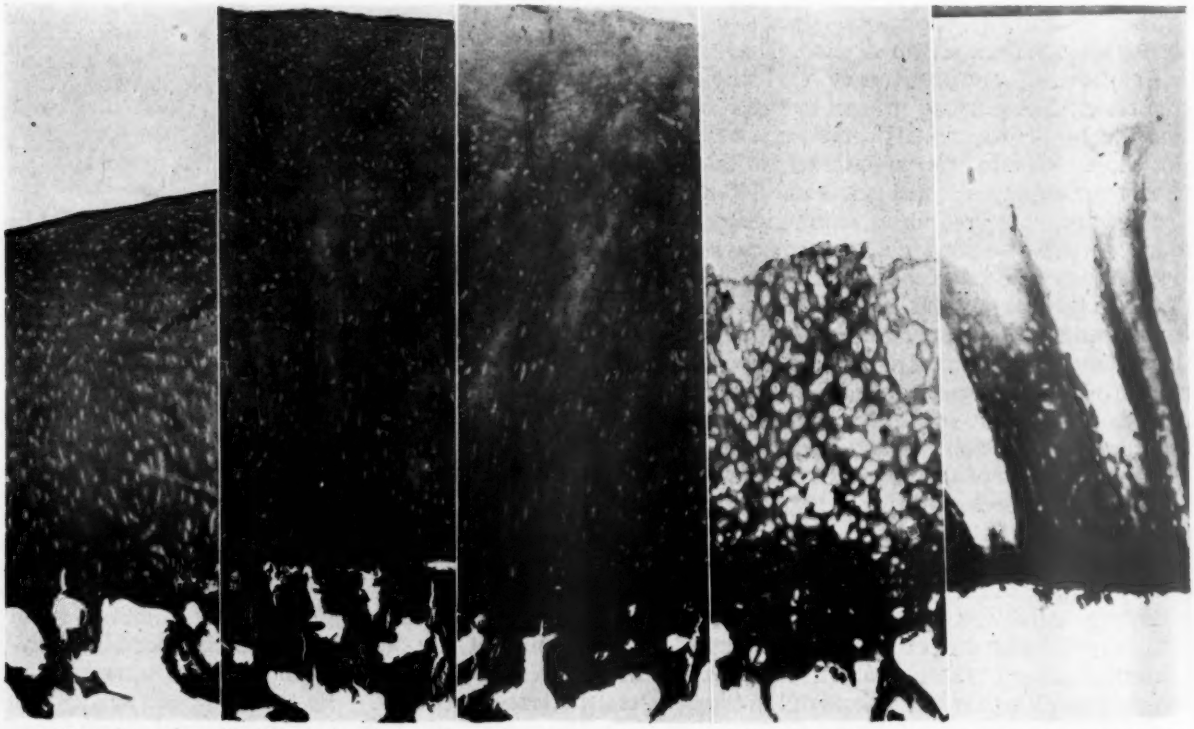
Results

Normal Findings (Figs 1*a*, 2*a*, 4*a*, and 4*f*).—The normal superficial zone of cartilage with transversely laid fibres contains collagen and a small amount of low polymer polysaccharide; high polymer is present in small quantity on the surface of the flattened cells only.



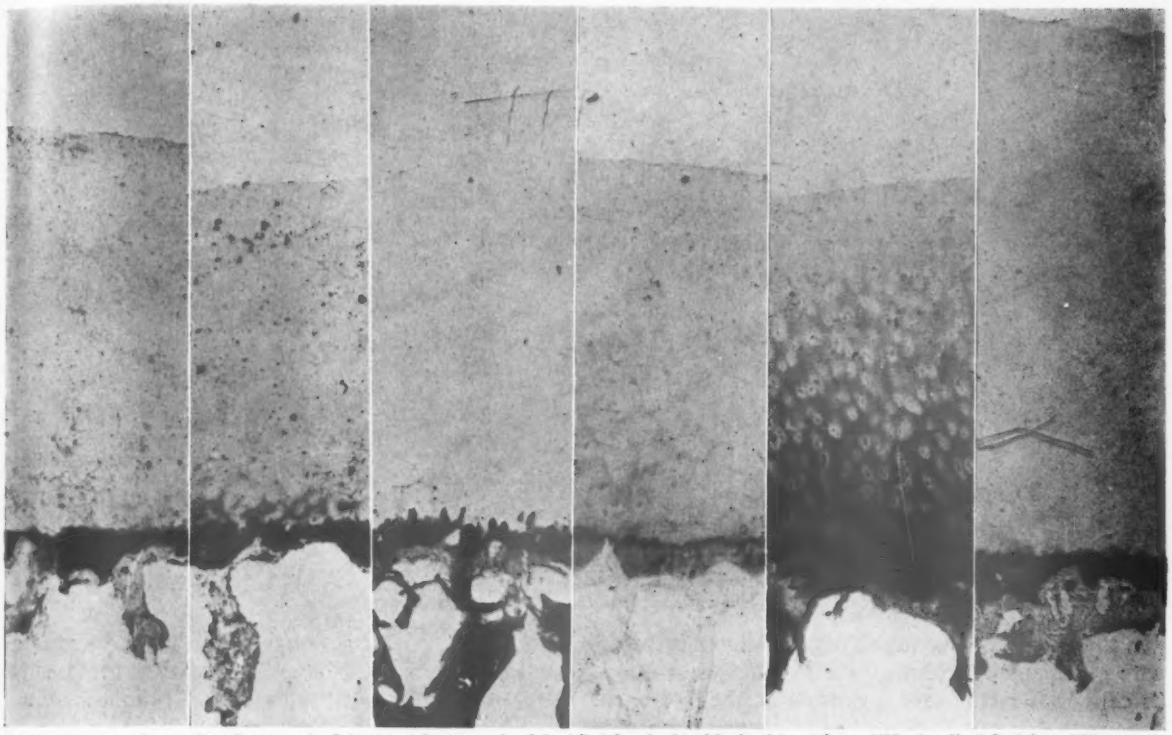
(*a*) Normal. (*b*) After hydrochloric acid. (*c*) After "Hyalase". (*d*) After collagenase. (*e*) After hydrochloric acid followed by collagenase. (*f*) After "Hyalase" followed by collagenase.

Fig. 1. (*a-f*)—Action of collagenase. × 29. Toluidine blue.



(*a*) Normal or after "Hyalase". (*b*) After hydrochloric acid. (*c*) After collagenase. (*d*) After "Hyalase" followed by collagenase. (*e*) After hydrochloric acid followed by collagenase.

Fig. 2. (*a-e*)—Action of collagenase. × 18. Van Gieson.

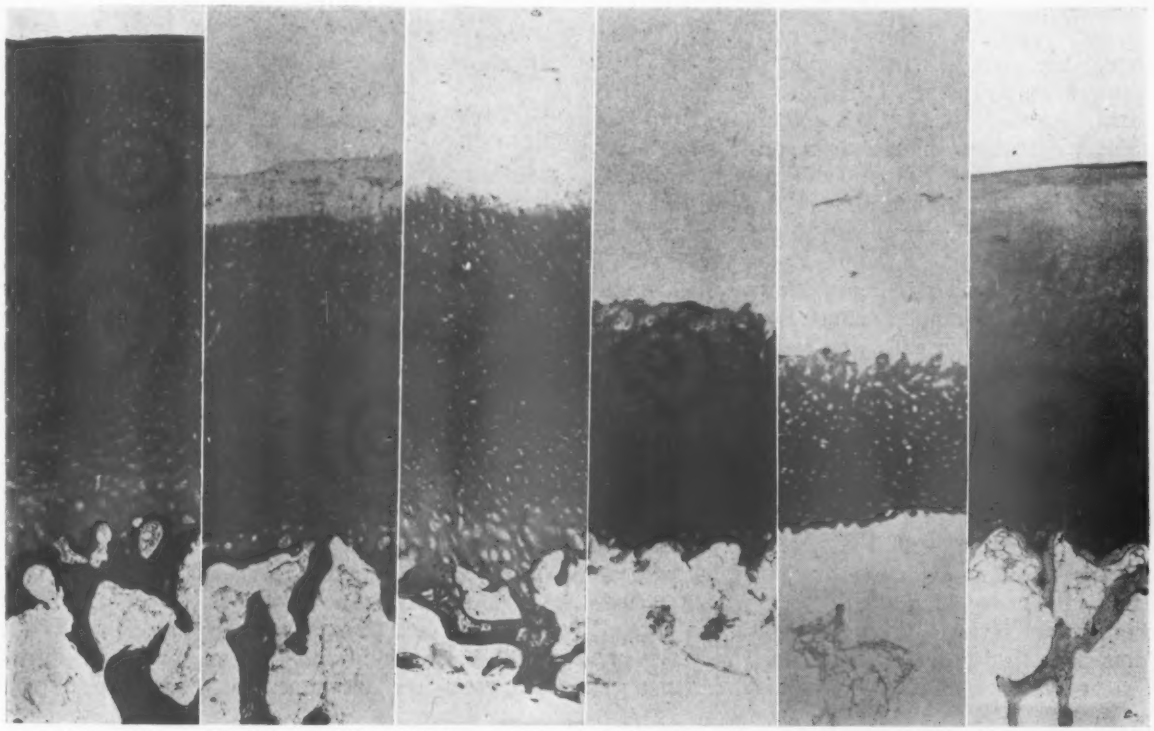


(*a*) After trypsin. (*b*) After trypsin followed by hydrochloric acid.* (*c*) After trypsin followed by collagenase. (*d*) After hydrochloric acid followed by "Hyalase".† (*e*) After "Hyalase" followed by hydrochloric acid. (*f*) After "Hyalase" and trypsin (effect same in either order).

Fig. 3. (*a-f*)—Action of trypsin and "Hyalase". × 24. Toluidine blue.

* Acid before trypsin removes the blue staining completely.

† For action of HCl + "Hyalase", see Fig. 1. Neither "Hyalase" nor trypsin affects Van Gieson staining.



(*a*) Normal. (*b*) Collagenase 24 hrs. (*c*) Collagenase 36 hrs. (*d*) Collagenase 60 hrs. (*e*) Collagenase 112 hrs. (*f*) Control—borate buffer—112 hrs.

Fig. 4. (*a-f*)—Detail of collagenase action. Paraffin sections after acid decalcification. × 23.
a-c) Van Gieson. (*d-f*) Periodic acid-Schiff, which distinguishes the calcified zone better.

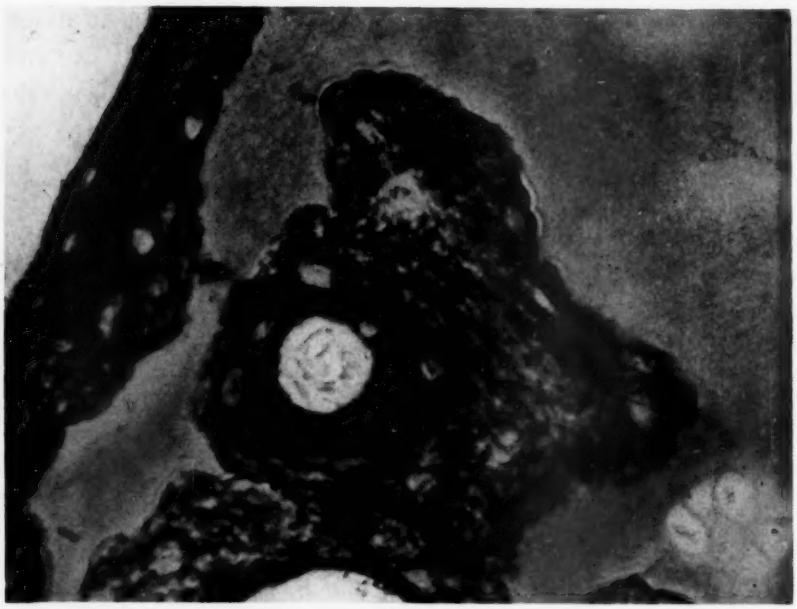


Fig. 5.—Detail of bone digestion. × 360. Van Gieson.

In the next zone the high polymer becomes much more conspicuous, forming pools diffusing around the cells, but rather less is present in the bands of fibres well away from the cells. Collagen is present throughout in very delicate fibrils whose existence and distribution is better shown by the configuration of the cells and their surrounding chondrin haloes and the lines along which normal cartilage splits in fractures, than by histological techniques which may introduce artefacts. In some cartilage in older people, the chondrin in the fibre bands falls off rapidly towards the basal zone, and may be nearly absent, leaving the cartilage eosinophil in the ordinary haematoxylin and eosin stain; the included cells remain strongly basophil and metachromatic.

The plane marking the apex of the calcified zone is a line of transition differing greatly from the tissue on either side. In the haematoxylin and eosin section it appears as a highly characteristic landmark of wavy granular purple, advancing more rapidly between the cells and held back opposite them and their pools of chondrin. The form of the line suggests the name "tidemark" which is brief and convenient: it marks the limit of calcification but is not actual calcium, since it is conspicuous in decalcified sections. The form of the line (Fig. 6) is suggestive of the front of a stream of calcium diffusing up from the bone, and is difficult to account for otherwise; further evidence for this is its frequent reduplication, recalling the Liesegang ring phenomenon which results from such diffusion into a gel: if this is correct, the name is fitting. The line is one of structural as well as topographical importance, since it marks the position of the plane of greatest weakness, clefts parallel to the joint surface occurring preferentially in this zone (Fig. 7) and far more readily than at the more obvious junction between cartilage and bone. The tidemark is not, however, a piece of cartilage which is embryologically, or otherwise structurally, different from the rest, but a plane that moves slowly away from the bone after the finish of growth and ossification in the adolescent articular lamella. Until then, the calcified cartilage is replaced by bone as soon as it is formed, but, with the formation of a stable bony plate at the base of the cartilage, a calcified band develops adjacent thereto. This is not strictly "provisional calcification" since it does not ordinarily ossify and, indeed, marks the end of progressive ossification. The "tidemark" represents the most recently calcified border of this calcified zone, a transition stage with on one side, cartilage that has passed through it, and on the other, ordinary hyaline cartilage that will shortly become calcified. In the middle it is free from staining for either high or low polymer polysaccharide, but on the borders are heavy granular deposits staining for calcium and both types of polysaccharide; even after removal of the calcium, the matrix retains the heavy basophilia that is so conspicuous in haematoxylin and eosin sections. The central part takes the picric acid component of Van Gieson's stain after decalcification.

The calcified zone stains with both P.A.S. and toluidine blue, though less metachromatically than in the uncalcified zone. The staining is uniform in contrast to the unevenness of the uncalcified zone,

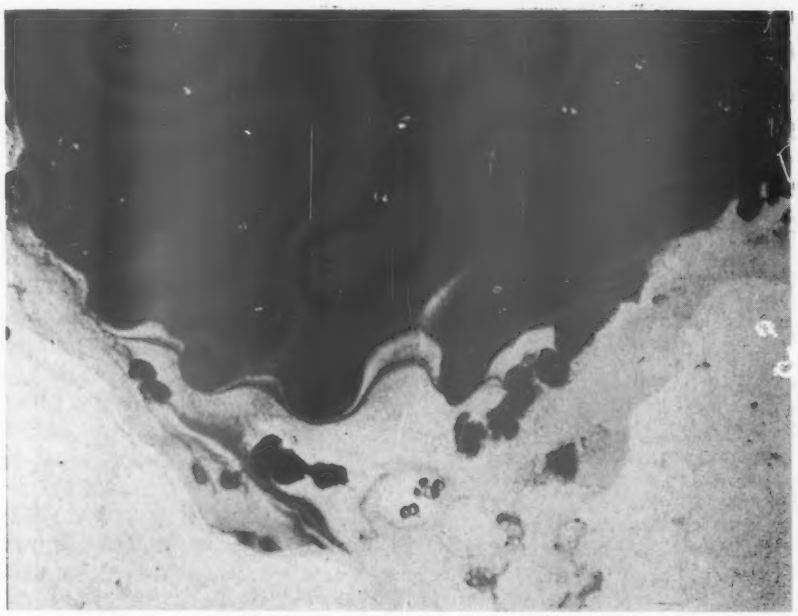


Fig. 6.—"Tidemark." ×77.
Toluidine blue.

Bone almost unstained, calcified cartilage pale grey, uncalcified cartilage dark grey. Original line of bone across bottom left corner, with "tidemark" reduplicated. New diffusion of calcium from osteophyte across bottom right corner nearly at right angles. "Tidemark" advancing between cells and their chondrin haloes, but held up opposite to them. Intense sharply limited haloes round cells in calcified zone.

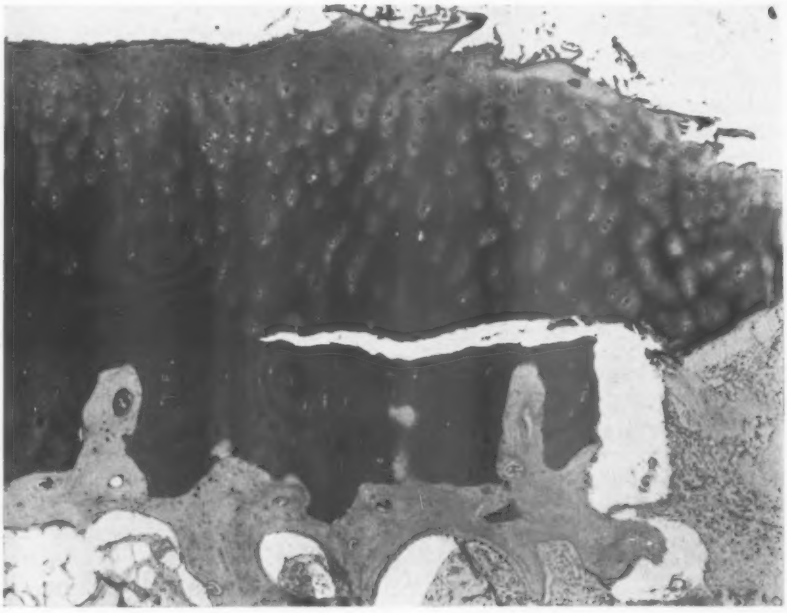


Fig. 7.—"Tidemark" as a zone of weakness. Fractured head of radius. × 42.
Periodic acid-Schiff.

Transverse fissure lies at apex of calcified zone. Positive staining of cement lines in bone just visible.

and around the surviving cells unusually deep haloes of polysaccharide are found with sharply defined borders (Fig. 6). This suggests that the diffusion of the chondrin is impeded compared with that in the uncalcified zone, because the molecules formed are larger, or the charges carried are different, or the calcified matrix is less permeable—another example of this change occurs when alginates are cross-linked by calcium. Calcium is present uniformly throughout the matrix. On the borders of the bone are found a double layer of a stain-free line and a granular layer of polysaccharide, somewhat resembling the tidemark, but without its weakness and never reduplicated.

In the bone, the lamellae contain collagen and calcium, but no polysaccharide can be demonstrated in them. The cement lines between systems, however, are low polymer polysaccharide without calcium or collagen. Woven bone fibres contain granular deposits staining for both calcium and polysaccharides (both by P.A.S. and by toluidine blue); osteoid is collagen only.

Action of Reagents

(*i*) *Hydrochloric Acid* (Figs 1*b*, 2*b*, and 4*a-f*).—As well as removing the calcium, the metachromasia of the calcified chondrin reverts to the intense metachromasia normal to the uncalcified part. This occurs regularly when the calcium is removed, but may also occur without decalcification, through the action of heat, storage in saline, and several other treatments.

(*ii*) *Hyaluronidase* (Figs 1*c*, and 3*d-f*).—The chondrin is completely leached out of the uncalcified cartilage, that in the cells and their haloes before that in the fibre belts. The calcified zone retains both its calcium and its chondrin, though the latter shows heat reversion of its metachromasia. *After decalcification*, however (Fig. 3*d*), the chondrin is broken down, that in the tidemark zone after that in the older calcified cartilage. The collagen is unchanged throughout.

(*iii*) *Collagenase* (Figs 1*d-f*, 2*c-e*, 3*c*, and 4*a-f*).—In all cases the superficial fibres containing neither calcium nor chondrin are digested. The bone and the calcified zone are quite untouched in the fresh material, the intervening zone being variably digested starting with the cell spaces and the tissue immediately around them.

After decalcification, the bone is dissolved both in fresh and in paraffin sections, the rather better preparation of the paraffin material and the slower action of the enzyme making it easier to see the detailed advance of the process. The calcified cartilage is dissolved in the fresh material completely and rapidly, but in the paraffin is less rapidly attacked than bone (Figs. 4*d* and 5).

After the use of "Hyalase" in the fresh material (Fig. 1*f*), the digestion of the uncalcified cartilage is much more rapid and complete. The effect begins in the cell spaces, and the cells and their haloes disappear while the denser fibre bands are untouched.

(*iv*) *Trypsin* (Fig. 3*a*, *b*, *c*, and *f*).—The collagen fibres are untouched and there is no decalcification. The chondrin is completely dissolved out of the uncalcified zone, that in the cells and their haloes before that in the fibre belts. In the calcified zone the chondrin becomes very densely stained to a bluish rather than a reddish purple, and this staining diffuses somewhat around the cartilage. After decalcification, the calcified zone chondrin is also removed by trypsin, but the dark purple material produced by trypsin in the fresh tissue is not removed by subsequent treatment with acid. After "Hyalase" the standard reaction is unchanged.

The uncalcified zone is rendered abnormally sensitive to collagenase by removal of the chondrin, just as it is by pre-treatment with "Hyalase", but the change in the calcified zone does not alter its resistance to collagenase.

Discussion

(1) Relation between Collagen and Calcium.—The presence of the calcium near the collagen appears to be a complete bar to the action of the collagenase. As we do not know the point of action of this enzyme, we can only assume that it is in some way covered by the calcium, possibly by the cross-linking of adjacent fibrillae or by the bending of the fibres: the presence of calcium ions does not affect the action of collagenase, and the effect is so easily reversible by dissolving the calcium that no great rearrangement of the protein appears to be possible.

(2) Relation between Collagen and Chondrin.—The position is less clear where chondrin is concerned. The collagenase effect is delayed when there is much chondrin, and is expedited when the chondrin is dissolved away, but the bar to action is not as absolute as in calcified tissue, possibly because the chondrin dissolves away from exposed surfaces more readily than the calcium. The relation may be one of mere proximity, the collagen fibres running through the polysaccharide in such a way that the enzyme cannot reach them, but the action of trypsin suggests possibilities of a direct link between the acid group of the polysaccharide and the amino groups of the protein (Haworth, 1947).

Support for this comes from the observation that the intensity of tolùidine staining—which is related to the acid groups of the polysaccharide and to the amino groups of the stain—is greatest near the cells from which the chondrin is produced and from which it diffuses, and becomes less when far away from them, where it might well have formed such linkages with protein and be unable to pick up the stain. Thus the action of trypsin in removing chondrin would be explained as the breaking of such a link.

(3) Relation between Chondrin and Calcium.—In the calcified zone, diffusion is impaired—as can be judged from the intensity and form of the haloes of the surviving cells in this zone, and from their frequent death in spite of their low oxygen requirements. Further, the degree of metachromasia is altered and reverts to that of normal cartilage when the calcium is removed, and we believe the metachromasia to be related to acidic groups and especially to sulphate groups in the chondrin. Again, the action of "Hyalase" is here held up just like that of collagenase, and is liberated by decalcification. Now, this zone is not made separately from the uncalcified zone or of different components, but is formed from it whenever bone and cartilage remain unaltered in contact with each other for a period of years; and the form of the line separating the calcified and uncalcified zones suggests that the change is due to diffusion of calcium. The interference with the two enzymes so caused can hardly be explained except by combination of the calcium with their substrates, since ionic and *p*H changes within reasonable limits do not upset the enzymes; and such combination will

also cover the changes in diffusion and metachromasia, and is known to occur in chemically similar alginates.

The action of trypsin on this zone includes the exposure of a large number of acidic groups from the chondrin without decalcification, as is shown by the intense toluidine blue staining. This suggests that some of the chondrin acid groups are concerned with linkage to protein, and some with calcium fixation. There are plenty of such groups available.

This chemical difference between the enzyme reactions of calcified and uncalcified cartilage is paralleled by the different methods adopted by the body for their removal. The uncalcified part of the articular cartilage is easily digested by polymorphonuclear leucocytes in purulent inflammation, whereas dead cartilage in aseptic situations is removed directly and inconspicuously by fibroblasts after the chondrin present has diffused away, being no longer re-formed by the dead cells. In calcified cartilage, however, as in bone, the method of removal is always by giant-cell ("osteoclastic") resorption, the calcium and the matrix being removed together; there is no previous removal, either by diffusion or by cellular action, of the chondrin in the cartilage.

Summary

(1) The action of collagenase on the fibres of lamellar bone is completely inhibited until the calcium is removed by acid; the strength and duration of the acid treatment is unlikely to have any hydrolytic effect on the collagen.

(2) The action of collagenase on the fibres of hyaline articular cartilage is delayed, though not inhibited, proportionally to the content of polysaccharide in the cartilage, and if this polysaccharide is removed the effect is complete and rapid.

(3) In the calcified zone of articular cartilage, where both chondrin and calcium are present, neither collagenase nor "Hyalase" has any action until the calcium is removed.

(4) The difference in enzyme reactions between calcified and uncalcified tissues is apparent *in vivo* in the methods used by the body for their breakdown.

(5) The evidence supports the view that the calcium and the collagen in particular, the chondrin and the calcium almost as certainly, and the chondrin and the collagen less clearly, are chemically linked rather than merely close neighbours.

We should like to thank Mr. Victor Trenwith for technical assistance, Mr. A. J. King for the photomicrographs, and the Yarrow Research Fund of the London Hospital for a grant towards expenses.

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Etudes biochimiques des affections rhumatismales
1. Observations sur les structures trabéculaires de l'os et du cartilage normaux

RÉSUMÉ

(1) L'action de la collagénase sur les fibres de l'os lamellaire est totalement inhibée jusqu'à ce qu'on ait extrait le calcium par un acide; il est peu probable que la force et la durée du traitement acide ait un effet hydrolytique sur le collagène.

(2) L'action de la collagénase sur les fibres du cartilage articular hyalin sans être inhibée est retardée proportionnellement à la teneur du cartilage en polysaccharide; quand on extrait le polysaccharide, l'action devient complète et rapide.

(3) Dans la zone calcifiée du cartilage articulaire, en présence tant de la chondrine que du calcium, aussi bien la collagénase que la "hyalase" n'agissent qu'après qu'on ait extrait le calcium.

(4) La différence entre les réactions enzymatiques dans les tissus calcifiés et non-calcifiés est apparente *in vivo* dans les méthodes employées par l'organisme pour les décomposer.

(5) Il y a des preuves montrant l'existence d'un lien chimique, plutôt que d'un rapport de voisinage, en particulier entre le calcium et le collagène, presque certainement entre la chondrine et le calcium et peut-être aussi entre la chondrine et le collagène.

Estudios bioquímicos de las afecciones reumáticas
1. Observaciones sobre las estructuras trabeculares del hueso y del cartílago normales

SUMARIO

(1) La acción de la colagenasa sobre las fibras del hueso lamelar queda completamente inhibida mientras no se extraiga el calcio con un ácido; la fuerza y la duración del tratamiento ácido no parece tener efecto hidrolítico sobre el colageno.

(2) La acción de la colagenasa sobre las fibras del cartílago articular hialino se ve retardada pero no inhibida proporcionalmente a su contenido de polisacarido; al extraer el polisacarido, el efecto es completo y rápido.

(3) En la zona calcificada del cartílago articular, en la presencia de la condrina y del calcio, tanto la colagenasa como la "hialasa" no actuan mientras no se extraiga el calcio.

(4) La diferencia entre las reacciones enzimáticas en los tejidos calcificados y sin calcificar es aparente *in vivo* en los métodos empleados por el organismo para su destrucción.

(5) Hay pruebas mostrando la existencia de un vínculo químico más bien que de vecindad, entre el calcio y el colageno en particular, entre la condrina y el calcio casi seguramente y, quizas, entre la condrina y el colageno.

FISTULOUS RHEUMATISM
A MANIFESTATION OF RHEUMATOID ARTHRITIS

BY

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The presence of fistulae discharging pus in the neighbourhood of a joint leads the physician to entertain the diagnosis of tuberculous infection, since this is the commonest chronic joint infection to break down in this way (*e.g.* Colvin, 1938; Steindler, 1938). Such fistulae are also seen in other types of long standing disease associated with tissue or bone necrosis, as in osteomyelitis, actinomycosis, or, elsewhere in the body, Krohn's disease. Cases have been recorded of such sinuses communicating with joints in granuloma inguinale (Donovan bodies) (Scott and others, 1944). Superficial necrobiotic lesions not infrequently break down and discharge

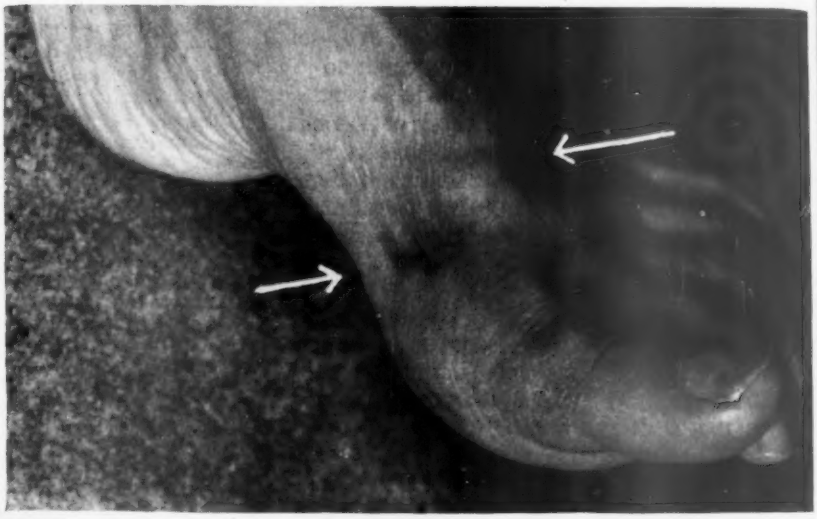
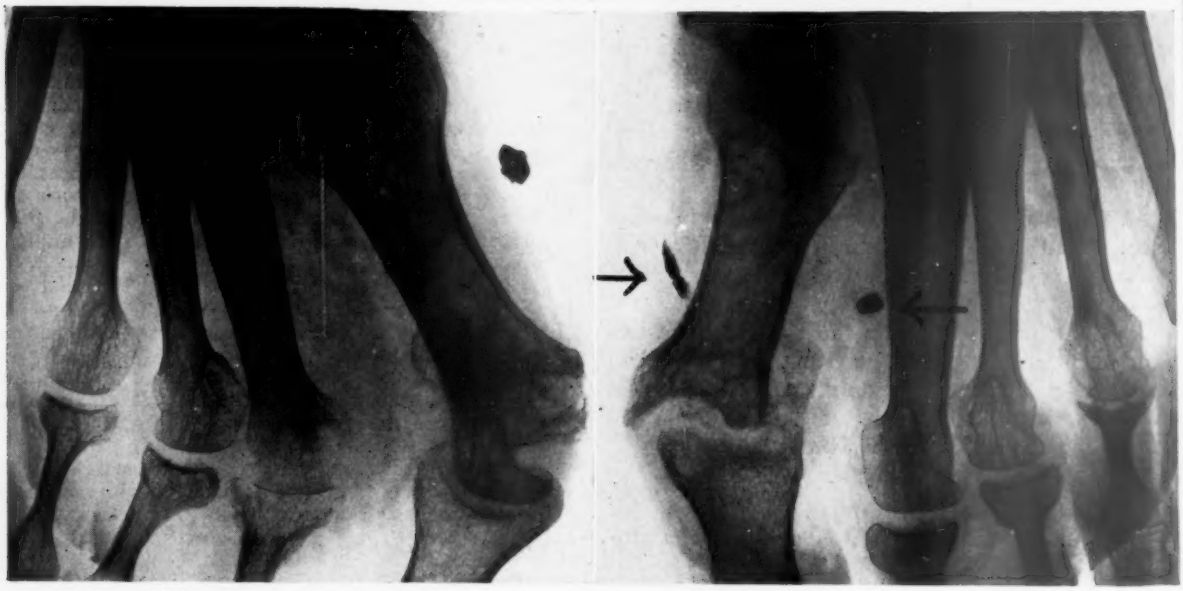


Fig. 1.—Case 1, left foot and *x* rays showing relationship of healed fistulae (marked by arrows) and underlying joint destruction.



their necrotic contents; this is seen with subcutaneous urate deposits, calcific deposits, and occasionally with the ordinary subcutaneous nodules of rheumatoid arthritis.

In the two cases detailed below, discharging sinuses appeared in the neighbourhood of joints which were affected by chronic rheumatoid arthritis. This is thought worth recording in the apparent absence of its previous description.

Case Reports

Case 1.—Female, aged 57, was first seen at the Canadian Red Cross Memorial Hospital on July 6, 1948.

History.—Rheumatoid arthritis had started in the fingers in January, 1944, and spread thence to most of the limb joints. Gold produced no improvement. Since 1946, small indolent violaceous lumps had appeared near the base of the big toe and some of the finger joints. Each of these took about 2 months to come to a head, and then discharged a thick greyish yellow material on and off for a period of 1 to 2 years, until finally healing occurred. These lumps were still appearing. The only pathogen isolated was *Staphylococcus pyogenes*; cultures for blastomycosis and other organisms were negative.

Examination.—Typical rheumatoid arthritis affected many joints.

Erythrocyte sedimentation rate 40-50 mm./hr (Westergren). Serum calcium, phosphorus, phosphatase, and uric acid normal.

Wassermann reaction negative.

Synovial fluid protein, 7·8 g. per cent., 18,500 cells per c.mm. with polymorphs 45 per cent., sugar 29 mg. per cent. (blood sugar, 58 mg. per cent.).

In relation to the joints showing most destruction radiologically (terminal interphalangeal left V and right I, proximal interphalangeal right II and IV in the hands and in the feet, metatarsophalangeal I right and left), there were scars of healed or healing fistulae, usually two to each joint (Fig. 1); those on the left little finger and right thumb (Fig. 2) were discharging pus from swollen, but not painful, granulation tissue nodules. The *x* ray showed cystic erosions and bone fragments lying in the soft tissue (Fig. 2). There was some swelling and slight reddening of the part. Biopsy of these two lesions showed no tuberculosis on culture. Histologically the area on the left little finger consisted of vascular

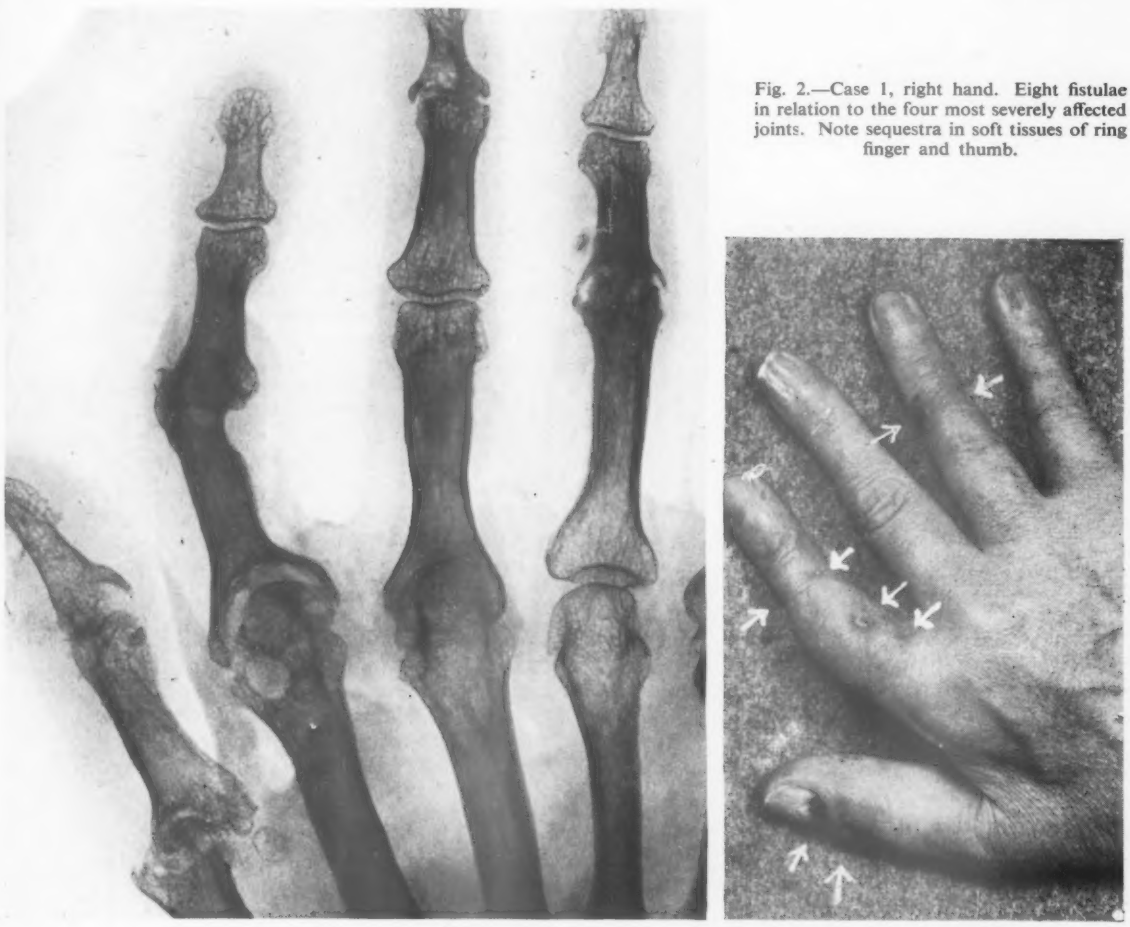


Fig. 2.—Case 1, right hand. Eight fistulae in relation to the four most severely affected joints. Note sequestra in soft tissues of ring finger and thumb.

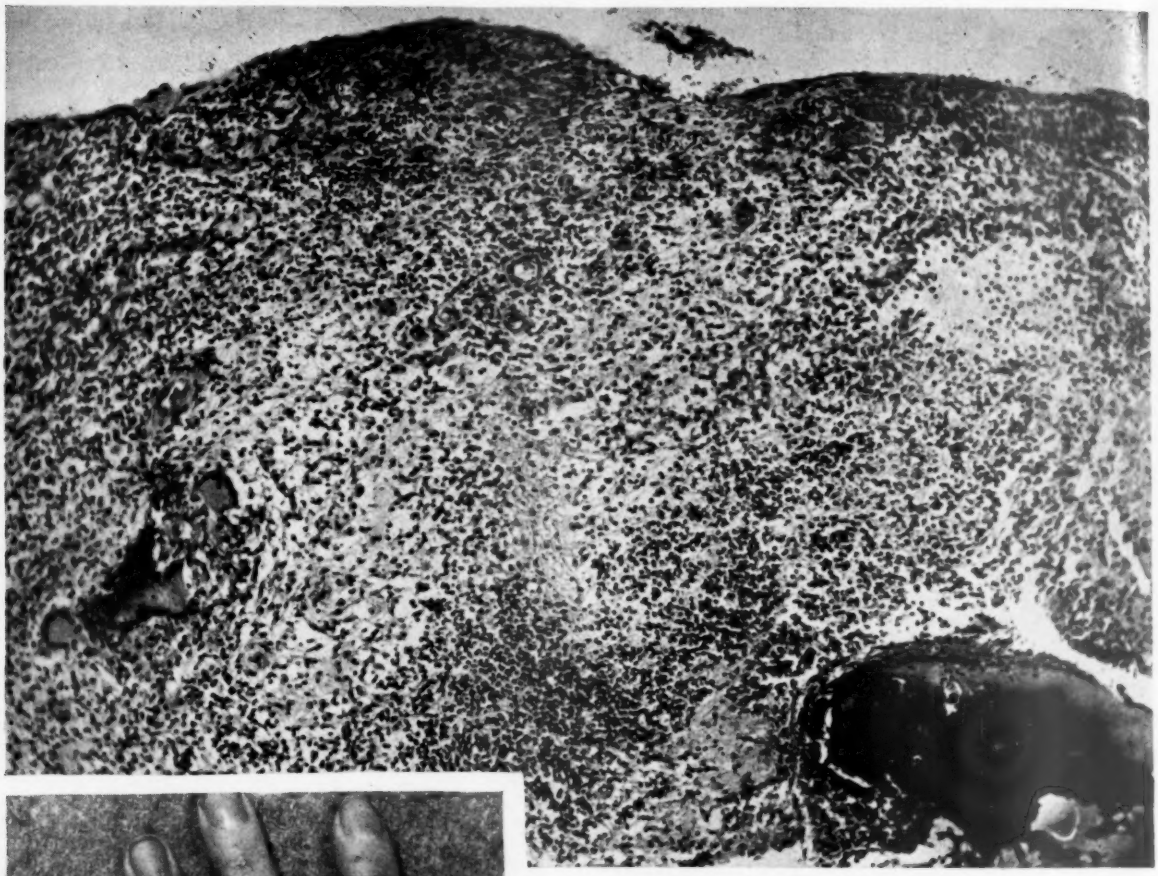


Fig. 3.—Case 1, granuloma (haematoxylin and eosin × 80) from left fifth finger, showing necrotic bone and cartilage, giant cells, lymphocytes, etc.

granulation tissue, including polymorphs, lymphocytes, and splinters of bone and cartilage, surrounded by foreign-body giant cells (Fig. 3). The nodule on the thumb (Fig. 4), which was biopsied before it broke down, showed a similar granulomatous formation beneath the skin blister.

Follow-up.—In 1952, 4 years later, the patient's condition had changed but little. Similar nodules were still appearing in fresh places, but in relation to the same joints; breaking down, discharging and then gradually healing again.

Case 2.—Female, aged 41, was first seen at the Postgraduate Medical School of London on January 8, 1952.

History.—Rheumatoid arthritis had started in the left wrist in 1944, and spread to the feet and hands; erythrocyte sedimentation rate 35 mm./hr (Westergren).

In 1946, a nodular swelling over the left first metatarsophalangeal joint broke down and discharged. This discharge continued until January, 1947, when the joint was opened and drained.

In February, 1947, she was treated for focal sepsis in another hospital.

In July, 1947, the nodules reappeared over the right and left big toe joints, broke down again, and discharged pus. In January, 1948, the head of the first left metatarsal bone was removed, together with all existing "nodules". However, 3 weeks after this operation, swelling and redness appeared over the right big toe; this eventually led to a fistula draining pus, which healed after 9 months. The right first metatarsophalangeal joint is now ankylosed.

Since that time, there have been four more flare-ups of these "nodules" in relation to the big toes; they followed the same pattern and showed little response to sulphonamide, chloromycetin, or penicillin, to which the patient

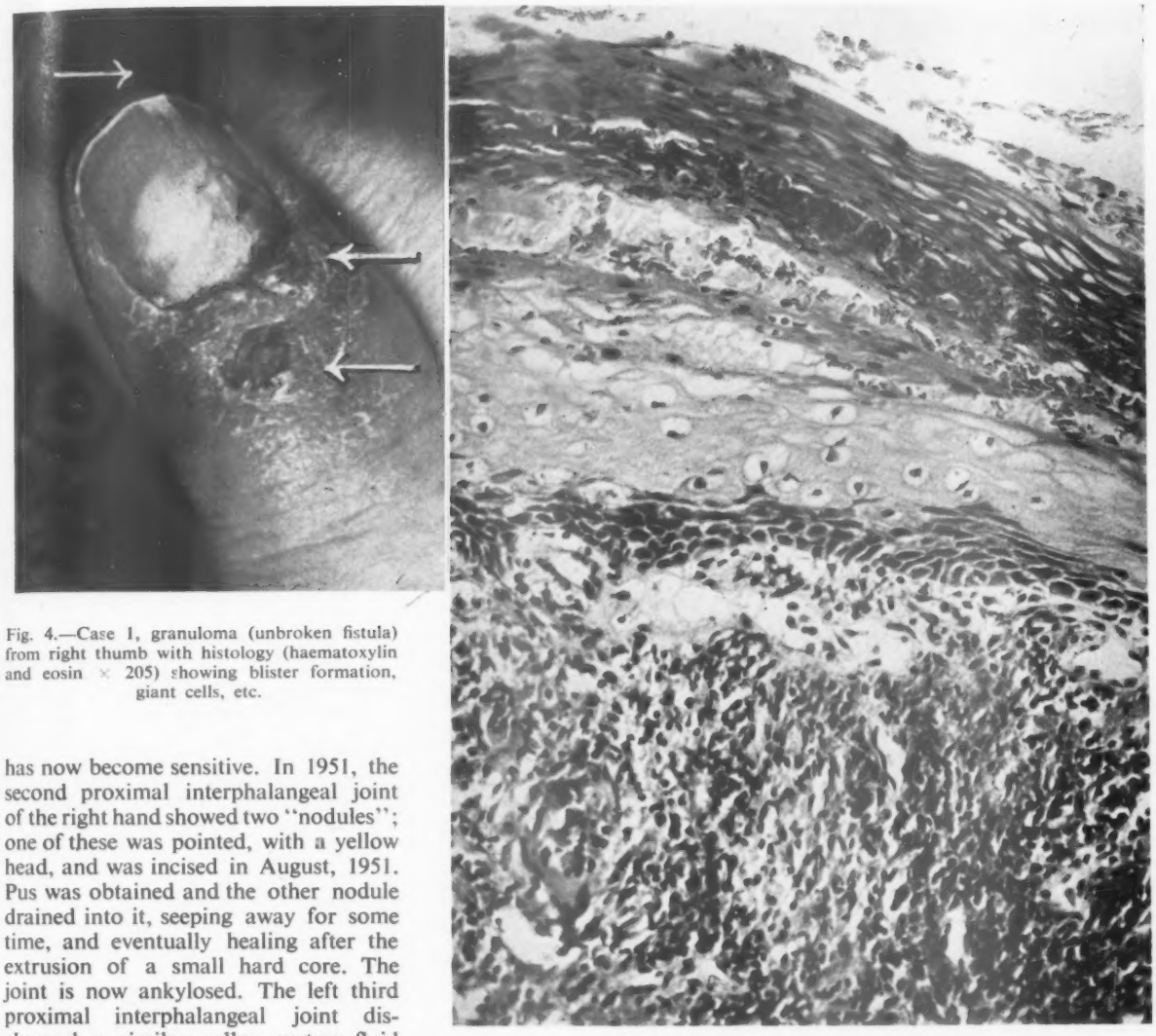


Fig. 4.—Case 1, granuloma (unbroken fistula) from right thumb with histology (haematoxylin and eosin × 205) showing blister formation, giant cells, etc.

has now become sensitive. In 1951, the second proximal interphalangeal joint of the right hand showed two "nodules"; one of these was pointed, with a yellow head, and was incised in August, 1951. Pus was obtained and the other nodule drained into it, seeping away for some time, and eventually healing after the extrusion of a small hard core. The joint is now ankylosed. The left third proximal interphalangeal joint discharged a similar yellow watery fluid in August, 1952. The other joints during these 8 years have been the seat of intermittent acute episodes of rheumatoid activity, each leaving some residual deformity, despite which the patient continued cheerfully with her occupation (school nursing).

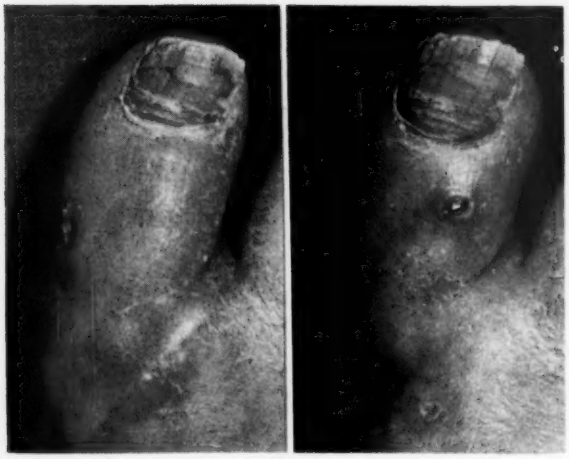
In July, 1952 (4 months before admission), an inflammatory swelling of the right palm appeared, which was thought to be a metastatic infection of the palmar bursa. This was opened at the wrist and drained pus intermittently.

Examination.—On admission to Hammersmith Hospital (in November, 1952), the patient showed classical rheumatoid arthritis with limitation of movement, deformity, soft tissue swelling, effusions of numerous joints, splenomegaly, and ordinary rheumatoid subcutaneous nodules (confirmed histologically) over the olecranon processes, on the Achilles tendon, the third left finger tendons, the palm and dorsum of left hand, and on the contact areas of the left fingers and thumbs. Some joints were ankylosed, including one (left terminal big toe joint) not associated with cysts or fistulae.

There were discharging sinuses at the right wrist and on the dorsal aspect of the right big toe (proximal phalanx). In the neighbourhood of this joint, over the right and left first metatarsophalangeal joints, and over the right second proximal interphalangeal joint, were seen the scars of healed fistulae (Fig. 5, overleaf).

Erythrocyte sedimentation rate varied between 24 and 52 mm./hr; serum calcium 10·2 mg. per cent., phosphate 2·2 mg. per cent. (as phosphorus), alkaline phosphatase 25 KA units, differential agglutination titre for sheep red cells 1 : 64; colloidal gold 5 units.

An *x* ray taken in the out-patient department in January, 1952, showed large bone cysts in numerous joints. Those most severely affected were those in relation to which fistulae had occurred, or were shortly about to appear, *i.e.* the head of the right proximal big toe phalanx, the head of the third left proximal phalanx, and



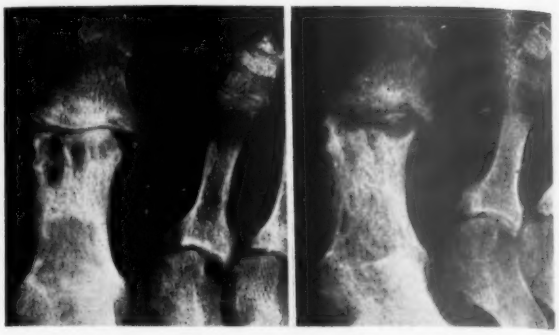
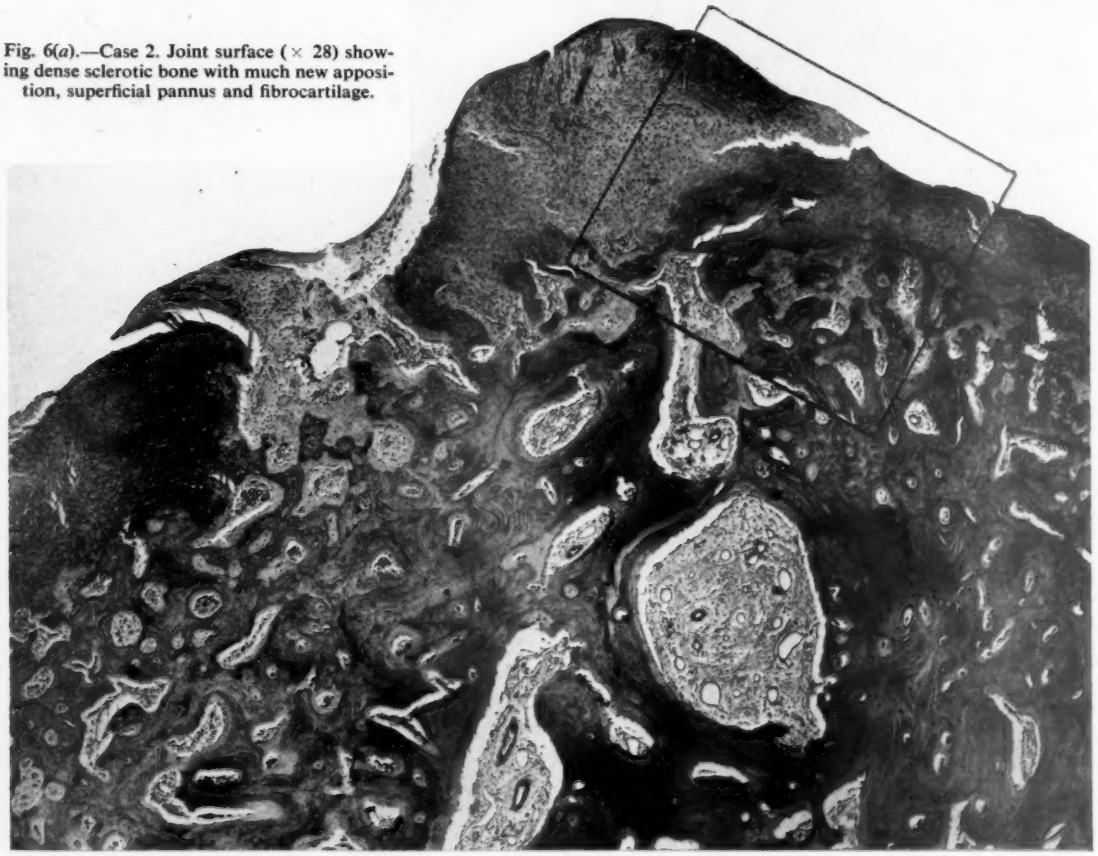


Fig. 5.—Case 2, new fistula forming in right big toe between January and October, 1952, in association with breakdown of bone cysts and sequestrum formation.

the head of the second right proximal phalanx. These we interpreted as herniations of synovial fluid and of rheumatoid granulation tissue into cancellous bone spaces exposed by erosion and attrition of cartilage. By November, 1952 (Fig. 5), the distal end of the right proximal big toe phalanx had undergone destruction, probably as a result of trauma to a structure weakened by the bone cysts. A sequestrum was visible in the joint cavity, and it is this, we suggest, which produced the subsequent abscess.

Fig. 6(*a*).—Case 2. Joint surface (× 28) showing dense sclerotic bone with much new apposition, superficial pannus and fibrocartilage.



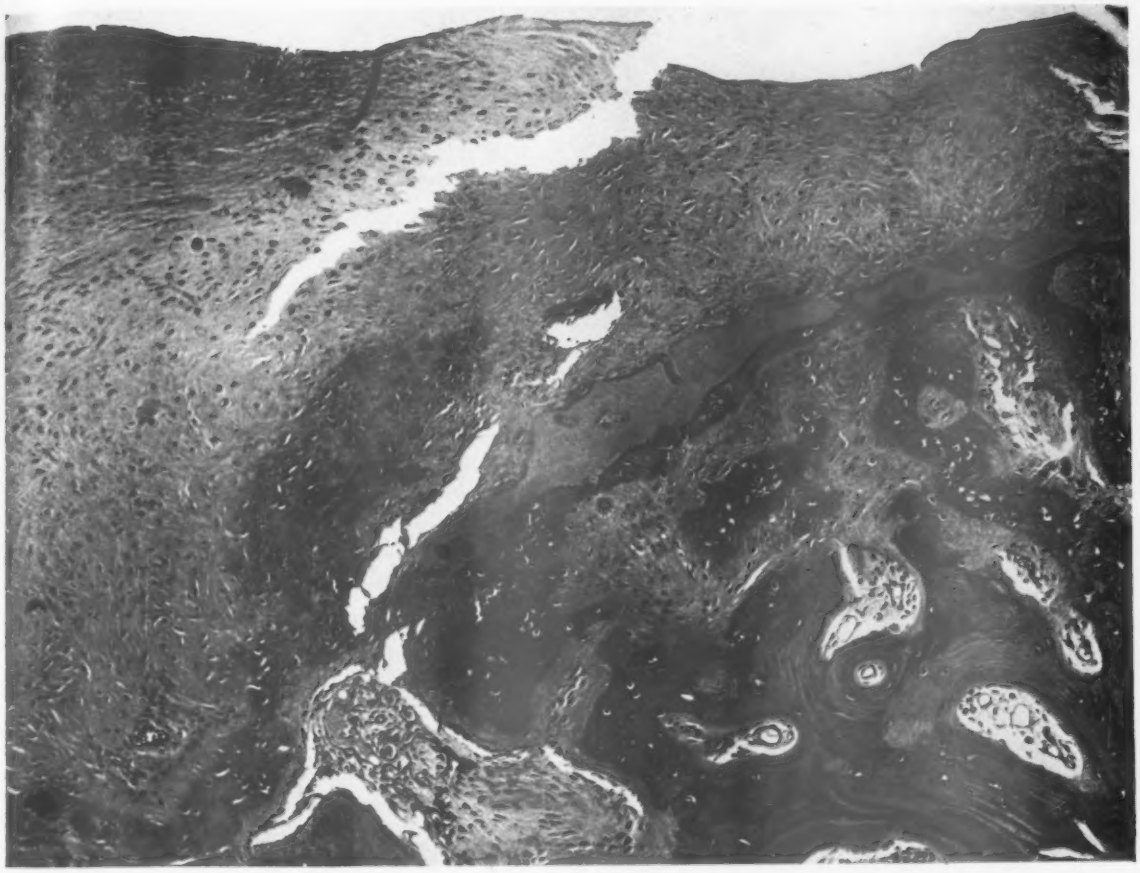


Fig. 6(*b*).—Case 2. Inset to 6(*a*) shows remains of hyaline cartilage, covered by pannus fibrocartilage, and underlain by woven bone (× 75).

In November, a culture from a healing fistula grew coagulase positive *Staphylococcus pyogenes* (penicillin resistant), but this was thought to be a superficial invasion, since another abscess, which appeared from the same joint, pointed a few weeks later (Fig. 5*b*), and was opened with sterile precautions, was found to be sterile on culture. Other cultures grew skin contaminants only. Investigations for tubercle bacilli, including culture and guinea-pig inoculation, were all negative.

In view of the inconvenience imposed by these fistulae, it was thought advisable to eradicate them surgically, and on December 1, 1952, after 2 days of penicillin injections, Mr. Stephenson removed the head of the proximal phalanx and the fistulous areas. No direct communication with the joint was found. The interior of the joint was full of soft vascular synovial processes typical of rheumatoid arthritis, but no naked sequestrum could be seen. Culture of the material removed grew *Staphylococcus pyogenes*. Histological examination (Figs 6*a* and *b*, and 7*a* and *b*, overleaf) showed that the bones taking part in the joint surface were extensively eroded. There was much new bone formation and sclerosis, side by side with areas of bone destruction by osteoclasts. The marrow spaces were in places invaded by granulation tissue containing large numbers of plasma cells and occasional lymphocytic foci: in places these intrusions formed large cysts, one of which contained a fragment of necrotic bone at its centre. Hyaline cartilage had almost disappeared (Fig. 6), and was covered by smooth surface pannus and fibro-cartilage. In places, new metaplastic fibro-cartilage formation was closing off the cancellous bone spaces, as is commonly seen in degenerative joint disease. Sections of synovial membrane (Fig. 7) showed a hyperplastic synovial membrane and a highly vascular connective tissue, containing small fragments of necrotic bone or cartilage, plasma cells, extravasated red blood cells, and aggregates of pyknotic nuclei, probably derived from polymorphonuclear leucocytes. There were a number of intact polymorphonuclear leucocytes in the superficial part of the membrane.

The picture was characteristic of that type of rheumatoid arthritis in which gross bone destruction has occurred: there was no evidence of any present pyogenic infection, nor were any organisms seen on Gram staining.

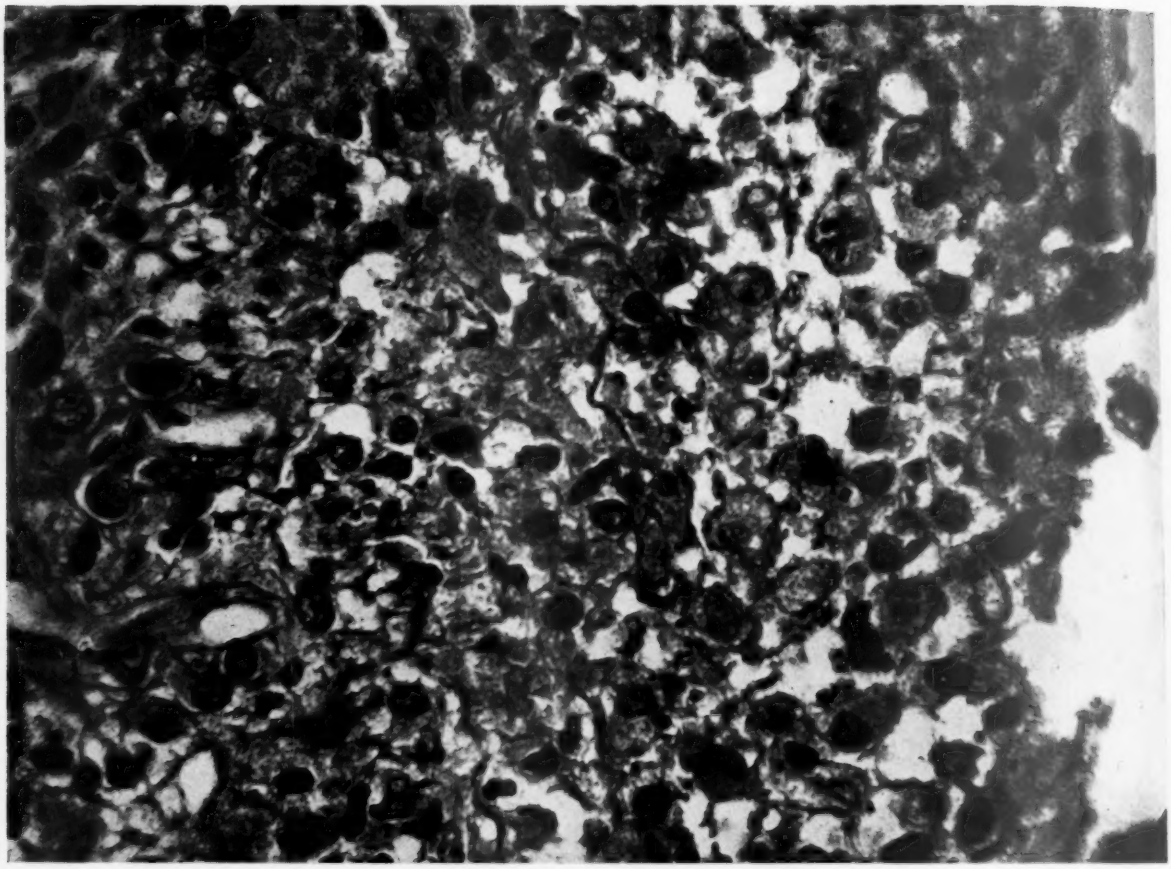


Fig. 7(*a*).—Case 2. Synovial membrane (haematoxylin and eosin × 700) showing hyperplastic surface and rich capillary granulation tissue with a few polymorphs.

Discussion

Both these patients suffered from chronic rheumatoid polyarthritis starting in the synovial membrane and later producing bone and cartilage destruction.

What factor was responsible in these patients for this peculiar manifestation in certain joints? One possibility is secondary staphylococcal infection. We have seen patients with rheumatoid arthritis with superadded suppurative arthritis due to *Staphylococcus pyogenes*: the clinical picture is typical of an acute suppurative arthritis with intense pain, heat, swelling, redness, fever, and leucocytosis, quite unlike these indolent, mild, recidivous lesions. Although on occasion *Staphylococcus pyogenes* was cultured from each case, a more careful investigation of a pointing and unbroken abscess was sterile on culture. It seemed to us that the staphylococcus isolated was a secondary invader of the fistulous opening and was unable to spread back through the granulation tissue to involve the joint. Metastatic staphylococcal joint infection seemed to be a possible but improbable cause of the fistulae, firstly, because there were none of the clinical signs of staphylococcal joint infection, and, secondly, because there was no histological evidence of pyogenic joint infection.

The following seems to be a more probable sequence of events:

Rheumatoid destruction of cartilage leads to the formation of bone "cysts" by exposure of cancellous bone spaces and the intrusion therein of synovial fluid under the pressure of movement, accompanied by rheumatoid granulation tissue and occasionally by necrotic fragments of bone. These bone cysts enlarge, and, together perhaps with the daily trauma of use, lead to microfractures and bone necrosis. Necrotic bone fragments are not uncommonly seen histologically engulfed in the synovium of banal rheumatoid arthritis surrounded by foreign body giant cells: they may occasionally be recognizable radiologically in uncomplicated rheumatoid arthritis, when they resemble the picture seen in Fig. 5. If numerous or large, they are extruded as foreign bodies; in joints near the surface, as here, these abscesses appear beneath the

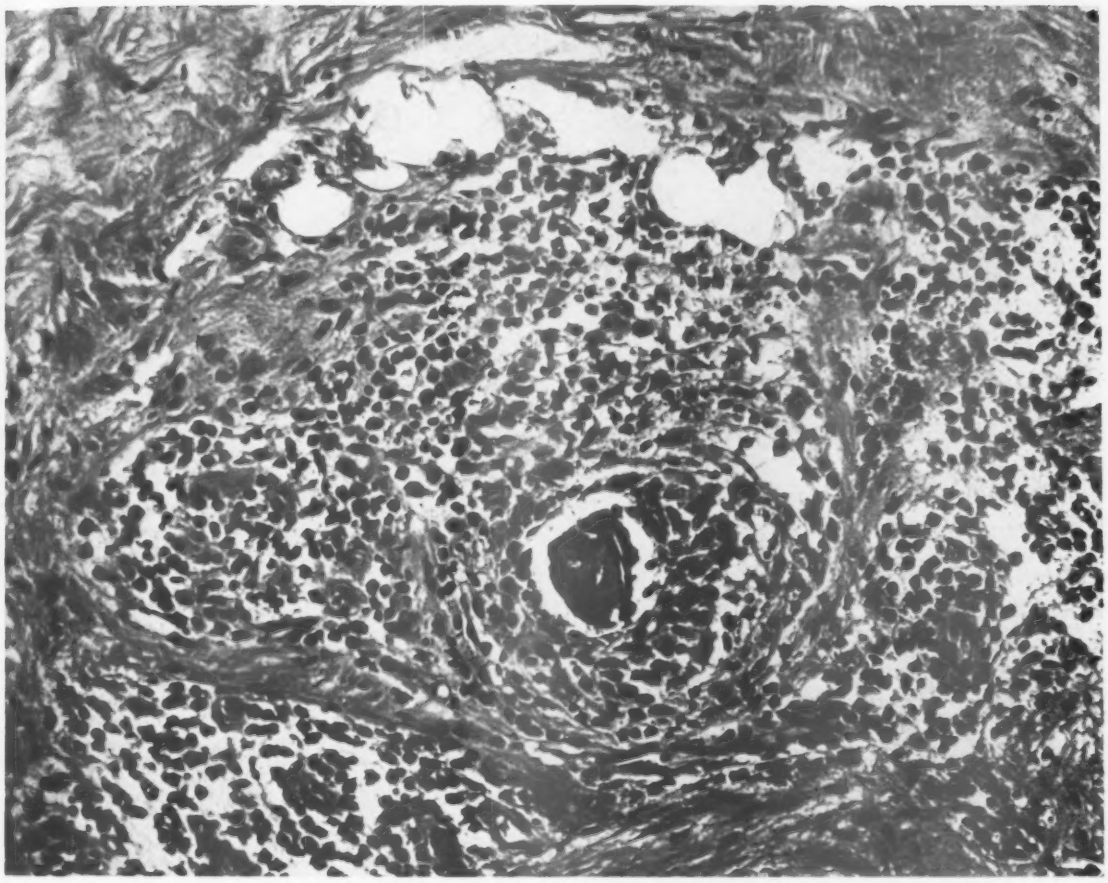


Fig. 7(*b*).—Necrotic bone fragment from middle of large bone cyst (haematoxylin and eosin × 210).

skin and rupture. All these abscesses are in the neighbourhood of severely eroded and comparatively superficial joints: biopsy reveals cartilage and necrotic bone in the granulation tissue.

Summary

Two cases of rheumatoid arthritis are described in which bone destruction led to the appearance, on the surface of the skin in the neighbourhood of the affected joints, of abscesses and fistulae containing fragments of necrotic bone and cartilage.

I am much indebted to Dr. F. E. Smith, of Rugby, and Mr. L. H. F. Walton, of Camberley, who referred these cases and allowed me to use their notes, and to Dr. H. S. Barber, of Buxton, for additional information. Mr. P. J. Fiske took the photographs.

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Rhumatisme fistuleux. Manifestation de l'arthrite rhumatismale

RÉSUMÉ

On décrit deux cas d'arthrite rhumatismale où la destruction osseuse mena à la formation au voisinage des articulations affectées d'abcès et de fistules cutanés contenant des fragments d'os et de cartilage nécrotique.

Reumatismo fistuloso. Manifestación de artritis reumatoide

SUMARIO

Se describe dos casos de artritis reumatoide en que la destrucción ósea motivó la formación en la vecindad de las articulaciones afectadas de abcesos y de fístulas cutáneas conteniendo fragmentos de hueso y de cartílago necróticos.

ULNAR DEVIATION OF THE FINGERS

BY

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The ulnar deviation of the fingers in rheumatoid arthritis has recently been dealt with in several publications (Bunnell, 1948; Fearnley, 1951; Rose and Kendell, 1952). Lush (1952) gives a list of the various aetiological factors so far described:

(1) Gravity,
(2) Pressure,
(3) Muscle imbalance,
(4) Unilateral laxity of capsules of metacarpophalangeal joints,
(5) Changed shape of joint surfaces,
(6) Disturbed function.

Another theory, put forward by Snorrason (1950, 1951), suggests that ulnar deviation is caused by the extensor tendons slipping off the knuckles.

The fingers of a normal hand when in a relaxed position form a direct continuation of the metacarpal bones. The fingers can then be moved in ulnar and radial directions both in flexion and in extension on the interphalangeal joints. In flexion the fingers tend to move slightly in the ulnar direction, while their capacity to move sideways diminishes as the flexion is increased, until in complete flexion, the collateral ligaments being fully extended, the fingers are locked.

Material and Methods

This investigation is based on 292 patients suffering from rheumatoid arthritis, whose metacarpophalangeal (mcp) joints were carefully examined. The age of the patients, the duration of the disease and of finger-joint symptoms, and the patients' occupation were noted. In order to ascertain the seriousness of the disease, the erythrocyte sedimentation rate and the objective symptoms in both wrists and elbows were taken into account.

For the purpose of the present investigation, cases were selected where a definite deviation in the resting position was coupled with the laxity of the mcp joints, the fingers then being fully flexed. A few cases in which, although there was ulnar deviation in the resting position, the functioning collateral ligaments forced the fingers back to the locked middle position, were excluded.

The material is divided into three groups: men, women, and children. Patients in whom the disease has started before the age of 14 are included in the third group, which thus also contains a few adults. Each group is subdivided, according to whether ulnar deviation was present or not.

Results

Ulnar deviation of the fingers was found in 14·6 per cent. of men and in 28·6 per cent.—nearly double as many—in women. In the third group it was rare (only 3·3 per cent.). The percentage of the cases taken collectively was 21·2; the detailed results are shown in the Table.

In the cases of ulnar deviation, the average age, and the duration of the disease and of finger joint symptoms, were all considerably higher. Judging by the higher erythrocyte sedimentation rate and by the more common parallel symptoms, in both wrists and elbows, the disease here was more serious. In all the cases there were objective symptoms in the metacarpophalangeal joints, swelling, hydrops, or subluxation. Limited finger extension was fairly common, and was due in most cases to the volar subluxation of the first phalanges. Subluxation of the metacarpophalangeal joints was present in joints II, III, V, IV, I (grouped according to the number of cases). This is also in accordance with the cases of ulnar deviation.

The displacement of the extensor tendons which Snorrason regards as a primary cause of ulnar deviation, seems to appear in the most serious cases only.

It seems also that Bunnell's intrinsic + position (1951) cannot be counted among the *causes* of ulnar deviation. As a rule, the deviation is present in both hands simultaneously, but when it is found in one hand only, it was equally common in either hand in males, while in females the right hand was more often affected. The patient's occupation does not seem to have any bearing on the development of ulnar deviation.

The following appears to be the process of development. Swelling and looseness in all parts of the

TABLE

PERCENTAGE INCIDENCE OF ULNAR DEVIATION OF THE FINGERS IN 292 CASES OF RHEUMATOID ARTHRITIS

Sex of Patients		Women		Men		Children		Total
Ulnar Deviation		Present	Absent	Present	Absent	Present	Absent	
Number of Cases		46	115	15	86	1	29	292
Average age (yrs)		42·0	38·2	45·3	36·8	16	11·6	36·4
Average duration of disease (yrs)		10·1	5·4	11·3	5·1	13	5·4	6·4
Average duration of finger joint symptoms (yrs)		9·3	4·2	9·1	3·7	13	5·8	5·4
Average erythrocyte sedimentation rate (mm./hr)		50·7	42·6	47·5	33·1	26	35·7	40·9
Objective symptoms	in wrists and elbows	43·5	19·1	40·0	16·3	100	44·8	26·0
	in metacarpophalangeal joints	100	58·3	100	43·0	100	44·8	62·0
Metacarpophalangeal joints	subluxation	65·2	2·6	73·3	1·2	100	17·2	17·5
	instability without subluxation	34·8	3·5	26·7	4·7	0	3·4	9·9
Limited finger extension		52·2	6·1	60·0	8·1	100	6·9	17·1
Displacement of extensor tendons		39·1	0	20·0	0	0	0	7·2
Ulnar deviation of fingers	right	21·7	—	26·7	—	0	—	4·8
	left	13·1	—	26·7	—	0	—	3·4
	both	65·2	—	46·6	—	100	—	13·0
Effect on ulnar deviation of flexion of metacarpophalangeal joints	increased	32·6	—	13·3	—	0	—	5·8
	diminished	8·7	—	13·3	—	0	—	2·1

metacarpophalangeal joint capsules and in collateral ligaments are caused by rheumatic inflammation. All the activities of daily living in which the use of both hands is required, tend to deviate the fingers in the ulnar direction, thus extending more the radial collateral ligaments. This extension is largest when the fingers, during this occupation, are in flexion at the metacarpophalangeal joints, when under normal circumstances the collateral ligaments are in tension. The radial interosseous and lumbrical muscles are extended, still retaining their acting capacity. Inactivity causes a general atrophy of the intrinsic muscles. In the early stages of the disease the patient is able to extend the fingers and move them, but owing to pain he seeks to avoid doing so. This causes a deformation of the metacarpophalangeal joint capsules so that ulnar deviation becomes the normal resting position of the fingers, but in most cases the fingers retain the ability to move in the radial direction.

The explanation why ulnar deviation is more common with females may be found in the fact that, apart from the more delicate structure of their bones, they are often obliged to go on with household work during the active stage of the disease, whereas the men have more opportunity for rest. The young patients with a chance of complete rest do not contract ulnar deviation, in spite of very serious rheumatoid arthritis.

That the collateral ligaments play an important part in preventing the development of ulnar deviation is shown by the following facts:

(1) In numerous cases of war casualties with ulnar and/or median nerve paralysis, ulnar deviation was never seen when the metacarpophalangeal joints were undamaged.

(2) In one case, treated by Dr. R. S. Mosiman and followed up by one of us, the patient had a severe traumatic claw hand. After resection of the collateral ligaments, a good flexion of the metacarpophalangeal joints was obtained; during a subsequent course of occupational therapy, ulnar deviation developed, which, in turn, was successfully treated by tendon transfer.

Summary

The incidence of ulnar deviation of the fingers has been examined in 292 unselected cases of rheumatoid arthritis. The condition was present in 14·6 per cent. of 101 males, in 28·6 per cent. of 161 females, and in 3·3 per cent. of thirty patients with infantile rheumatoid arthritis. It seems to have been caused by a relaxation of the collateral ligaments owing to rheumatic inflammation, coupled with the small activities of daily living which tend to deviate the fingers in the ulnar direction.

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Déviation cubitale des doigts

RÉSUMÉ

On étudia la fréquence de la déviation cubitale des doigts dans 292 cas pris au hasard d'arthrite rhumatismale. On trouva ce symptôme dans 14,6% des 101 cas masculins, dans 28,6% des 161 cas feminins et dans 3,3% des 30 cas d'arthrite rhumatismale infantile. La déviation semble être due au relachement des ligaments latéraux, consécutif à l'inflammation rhumatismale, associé aux petits mouvements de la vie quotidienne tendant à faire tourner les doigts en dedans.

Desviación cubital de los dedos

SUMARIO

Se estudió la incidencia de la desviación cubital de los dedos en 292 casos, tomados al azar, de artritis reumatoide. Encontrose este trastorno en el 14,6 por ciento de 101 casos masculinos, en el 28,6 por ciento de 161 casos femeninos y en el 3,3 por ciento de 30 casos de artritis reumatoide infantil. Este trastorno parece haber sido causado por un relajamiento de los ligamentos colaterales, consecutivo a la inflamación reumática asociada con los pequeños movimientos de la vida ordinaria en que los dedos tienden a desviarse en la dirección cubital.

HYDROCORTISONE ADMINISTERED ORALLY IN RHEUMATOID ARTHRITIS

BY

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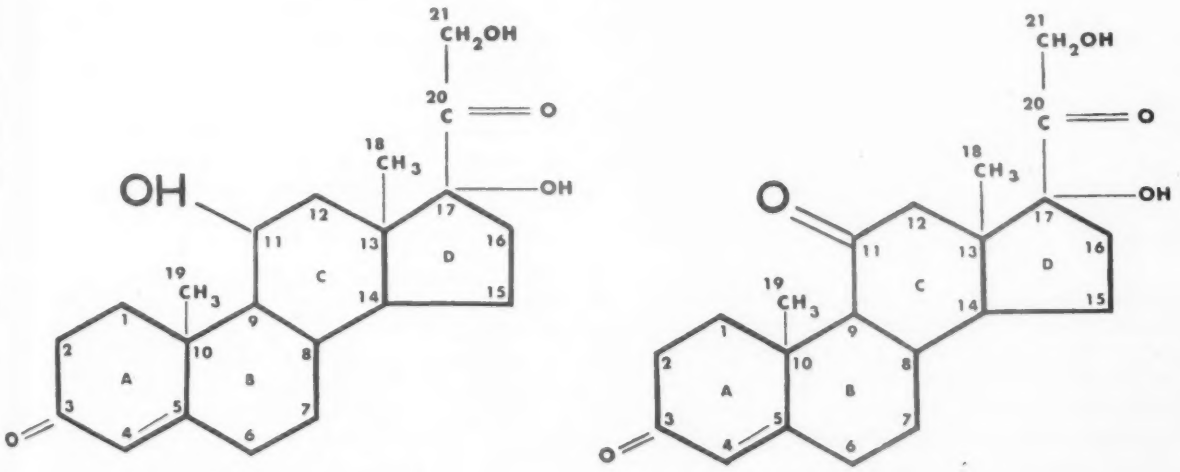
Of the various steroid substances which have been isolated from the adrenal cortex, thus far only two, cortisone (17-hydroxy-11-dehydrocorticosterone: Kendall's Compound E) and hydrocortisone (17-hydroxycorticosterone: Kendall's Compound F), have shown definite antirheumatic activity. These two hormones are closely related chemically, differing in but a single structural detail: cortisone has a ketone group, while hydrocortisone has a hydroxyl radical placed at the eleventh carbon position in the steroid nucleus (Figure). There is convincing evidence from laboratory experiments, however, to suggest that hydrocortisone may be the principal glycogenically active steroid derived from the adrenal cortex, that it probably participates more than cortisone in tissue reactions under conditions of stress (Conn and others, 1951; Jacobsen and Pincus, 1951; Pincus, 1949), and that its physiologic potency in animals is about twice as great as that of cortisone (Ingle and Kuizenga, 1945; Ingle, 1946; Pabst and others, 1947). Moreover, data are rapidly accumulating from clinical investigations which indicate that hydrocortisone is, milligram for milligram, distinctly more powerful than cortisone in anti-inflammatory and anti-allergic activity, and that it may often be employed more advantageously as a therapeutic agent.

Preparations of Hydrocortisone

Two forms of hydrocortisone are available commercially: the pure hormone—hydrocortisone (free alcohol)—herein referred to as hydrocortisone; and an ester—hydrocortisone acetate. The two compounds must be carefully distinguished as they differ decidedly in solubility and absorption, and in therapeutic effectiveness when given orally. Hydrocortisone is much more soluble in various media and, when administered by mouth, may be nearly twice as potent as the acetate ester in reducing the manifestations of rheumatoid arthritis



(a) HYDROCORTISONE
(17-Hydroxycorticosterone: Kendall's Compound F)

(b) CORTISONE
(17-Hydroxy-11-Dehydrocorticosterone: Kendall's Compound E)

Figure.—Chemical structure of (a) hydrocortisone and (b) cortisone.

(Boland, 1952a). Hydrocortisone acetate is highly efficient, however, in temporarily alleviating signs of articular inflammation when injected locally into a joint.

Investigations

When long-term studies revealed that cortisone acetate failed to provide satisfactory degrees of improvement in an appreciable percentage of patients with rheumatoid arthritis, interest was aroused in finding an agent which might be used more advantageously. Better results with cortisone have been prevented mainly because objectionable endocrine complications have intruded frequently during treatment, particularly in patients with more severe disease who have required large doses of the hormone for satisfactory rheumatic control. Too often the appearance of adverse reactions has necessitated reduction of dosage to levels insufficient for adequate relief. Obviously a steroid with greater anti-inflammatory power but without a correspondingly greater tendency to produce undesired effects, or one with equal therapeutic potency and fewer liabilities, should provide superior clinical results.

In the spring of 1951 we began studies to ascertain the relative therapeutic efficiency of hydrocortisone and cortisone acetate when the substances were administered orally to patients with rheumatoid arthritis. As supplies of hydrocortisone were greatly restricted, pilot investigations were done at first to compare

(*a*) the maintenance doses of the hormones needed to uphold similar degrees of clinical improvement, and

(*b*) the response of rheumatic manifestations to initial suppressive doses of the compounds when they were administered in equivalent milligram doses.

Later, as larger quantities of material were provided, prolonged treatment studies with hydrocortisone were undertaken; these are still in progress, but have now proceeded for periods long enough to allow some provisional data.

Results

Patients transferred from Cortisone Acetate to Hydrocortisone Therapy.—In preliminary investigations, conducted by transferring the treatment of patients from one preparation directly to another, comparisons were made of the maintenance doses needed to support similar degrees of clinical improvement (Boland, 1952a, b, c). These studies disclosed that the maintenance requirements for hydrocortisone were uniformly less, and it was estimated that the hormone was at least 50 per cent. more effective, milligram for milligram, than cortisone acetate. Dosage ratios of hydrocortisone to cortisone acetate ranged from 1 : 1·43 to 1 : 1·7, with an average of 1 : 1·59 for the group tested. Comparisons made between cortisone (free alcohol) and cortisone acetate failed to reveal any significant differences in potency. Some observations made during the study suggested that endocrine complications from effective therapeutic amounts of hydrocortisone might not be as frequent or as marked; signs of hormone excess displayed by several patients during cortisone acetate administration either lessened or disappeared following transfer to smaller, but equally effective, doses of hydrocortisone.

Longer-term investigations have since been made in 44 patients transferred from cortisone acetate to hydrocortisone. These patients received cortisone acetate continuously for periods ranging from 10 to 138 weeks (average 60). Their maintenance therapy was well stabilized and the greatest degree of improvement consistent with the avoidance of seriously objectionable side-effects was maintained. Following transfer of treatment, the patients have, to the time of this analysis, taken hydrocortisone uninterruptedly for periods ranging from 12 to 66 weeks (average 26).

The maintenance doses of hydrocortisone needed to uphold equal or greater degrees of clinical improvement have been materially less than for cortisone acetate in most cases; the dosage has been lower in forty of the 44 patients (91 per cent.), approximately the same in four (9 per cent.), and greater in none. For the entire group, the daily maintenance dosage has averaged 44·5 mg. for hydrocortisone and 62·3 mg. for cortisone acetate. In spite of smaller milligram doses, better antirheumatic control has been supported with hydrocortisone in two-thirds of the patients. Six patients with severe, one with moderately severe, and one with moderate disease have improved from inadequate to adequate levels since transfer.

In order to compare endocrine complications from the two steroids, many patients were purposely selected for transfer to hydrocortisone because they exhibited signs of hormone excess during cortisone acetate administration. Among the 44 patients studied, 31 (70 per cent.) displayed adverse reactions to cortisone acetate. After transfer to hydrocortisone in smaller milligram doses, the overall incidence of adverse reactions was lowered from 70 to 52 per cent. Of more significance, however, was the fact that one or more abnormal signs either lessened substantially or disappeared in 22 of the 31 patients (71 per cent.). Certain individual reactions tended toward correction more than others:

nervous symptoms disappeared or were reduced in thirteen of fifteen patients, oedema in nine of fifteen patients, and moon facies and supraclavicular fat pads in nine of 23 patients; but generalized obesity was corrected in only two of nine patients, and signs such as hypertrichosis (twelve patients) and irregular glycosuria (two patients) were not changed during the periods of observation.

Patients treated initially with Hydrocortisone.—In a preliminary study, ten patients with rheumatoid arthritis were given hydrocortisone as initial treatment in dosages similar to those customarily employed for cortisone acetate (Boland and Headley, 1952). During these short-term investigations it was noted that the general pattern of improvement corresponded closely to that which results from cortisone acetate. With the same milligram doses, however, the onset of relief from hydrocortisone was faster and more striking, subsequent improvement progressed more quickly, and elevated erythrocyte sedimentation rates diminished more rapidly and regularly. These observations suggested that smaller doses of hydrocortisone given at the beginning of treatment might accomplish satisfactory suppression of the disease.

Subsequently, long-term studies have been instituted, using hydrocortisone as the only form of therapy. To date sixteen patients have received the hormone continuously for more than 12 weeks, some for as long as 30 weeks. The same general plan of treatment as that used for cortisone acetate was followed. This involved three stages:

(1) initial suppressive doses,
(2) gradual dosage reduction,
(3) maintenance therapy.

The smallest daily amount of hormone capable of controlling the disease manifestations adequately, but not necessarily completely, was considered the optimal maintenance dose for long-term therapy. Because hydrocortisone is rapidly absorbed and its effects are rapidly dissipated, the total daily dose was divided routinely into four parts, taken at mealtimes and at bedtime.

The initial suppressive doses employed for these sixteen patients were substantially less than those ordinarily prescribed for cortisone acetate in cases with corresponding degrees of disease severity. Initial daily doses of 60 to 80 mg. for severe cases, 50 to 70 mg. for moderately severe cases, and 40 to 60 mg. for moderate cases provided rapid and progressive improvement comparable to that noted with customary larger doses of cortisone acetate. With these doses euphoric reactions did not occur and nervous symptoms were uncommon; one patient experienced insomnia and "tenseness" with suppressive doses of 50 mg. daily, but these disappeared when maintenance doses of 35 mg. daily were established.

The daily amounts of hydrocortisone required to maintain satisfactory improvement in these patients were, in general, distinctly smaller than those usually needed with cortisone acetate; maintenance doses averaged 47 mg. for severe cases, 38 mg. for moderately severe cases, and 30 mg. for moderate cases. Adequate improvement (marked or very marked) was maintained in fifteen of the sixteen patients, and so far only three have developed untoward signs of hormone excess, mild in each instance. These data, as well as the deductions derived from them, must, however, be considered as preliminary and tentative, as this part of the study now includes only a few patients followed for a relatively short time; and it may be anticipated that improvement may deteriorate in some patients when treatment is continued for longer periods.

Summary

Hydrocortisone (Compound F) was administered orally to two series of patients with rheumatoid arthritis. One group (44 cases) was given hydrocortisone after periods ranging from 10 to 138 weeks (average 60) during which they had received cortisone acetate (Compound E). A second group (sixteen cases) was treated with hydrocortisone from the beginning.

These clinical investigations led to the following conclusions:

(1) The antirheumatic activity of hydrocortisone is greater than that of cortisone or cortisone acetate when the substances are given orally in equivalent doses.

(2) The daily doses required for initial suppression of the disease and for maintenance of satisfactory improvement are appreciably smaller with hydrocortisone. Milligram for milligram, the antirheumatic potency of hydrocortisone may be estimated as at least 50 per cent. greater than that of cortisone or cortisone acetate, and as approximately 100 per cent. greater than that of hydrocortisone acetate.

(3) The dissociation between anti-inflammatory and certain other endocrine effects seems to be greater with hydrocortisone than with cortisone acetate, so that with smaller, but equally effective, doses of hydrocortisone, unwanted signs of hormone excess may be more easily prevented or controlled.

(4) As an agent for prolonged systemic administration in responsive chronic diseases such as rheumatoid arthritis, hydrocortisone appears to have therapeutic advantages over cortisone acetate.

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Hydrocortisone par voie buccale dans l'arthrite rhumatismale

RÉSUMÉ

On administra de la hydrocortisone (Composé F) par voie buccale à deux groupes de malades atteints d'arthrite rhumatismale. Un groupe (44 cas) se composait de malades antérieurement traités par l'acétate de cortisone (Composé E) pendant des périodes de 10 à 138 semaines (60 en moyenne) tandis que l'autre groupe (16 cas) n'avait pas subi ce traitement.

Ces recherches cliniques menèrent aux conclusions suivantes:

(1) L'action anti-rhumatismale de la hydrocortisone est plus forte que celle de la cortisone ou de l'acétate de cortisone, pourvu qu'on administre ces substances par voie buccale et à des doses équivalentes.

(2) Les doses quotidiennes nécessaires pour obtenir la suppression initiale de la maladie et pour maintenir une amélioration satisfaisante sont appréciablement plus faibles pour la hydrocortisone. Milligramme pour milligramme, le pouvoir antirhumatismal de la hydrocortisone peut être estimé comme étant au moins 50% supérieur à celui de la cortisone ou de l'acétate de cortisone et à peu près 100% supérieur à celui de l'acétate de hydrocortisone.

(3) La dissociation entre l'effet anti-inflammatoire et les autres effets endocrines semble plus accentuée avec la hydrocortisone qu'avec l'acétate de cortisone, de manière que des doses plus faibles mais aussi efficaces de hydrocortisone sont suffisantes pour éviter ou bien controler plus facilement les manifestation néfastes de l'excès d'hormone.

(4) En tant qu'agent thérapeutique exigeant l'administration interne prolongée dans les maladies chroniques sensibles à son action, telles que l'arthrite rhumatismale, la hydrocortisone semble l'emporter sur l'acétate de cortisone.

Hidrocortisona por vía oral en la artritis reumatoide

SUMARIO

Se administró hidrocortisona (Compuesto F) por vía oral a dos grupos de enfermos con artritis reumatoide. Cuarenta y cuatro enfermos previamente tratados con acetato de cortisona (Compuesto E) durante períodos de 10 a 138 semanas (un promedio de 60) formaron un grupo; dieciseis casos sin tratamiento hormonal previo formaron el otro.

Estas investigaciones clínicas dieron lugar a las conclusiones siguientes:

(1) La acción antirreumática de la hidrocortisona es más fuerte que la de la cortisona o del acetato de cortisona cuando se administra estas substancias por vía oral en dosis equivalentes.

(2) Las dosis diarias de hidrocortisona necesarias para obtener la supresión inicial de la enfermedad y para mantener una mejoría satisfactoria son apreciablemente más pequeñas. Miligramo por miligramo, el poder antirreumático de la hidrocortisona parece superar al de la cortisona o del acetato de cortisona de un 50% al menos y al del acetato de hidrocortisona de cerca de un 100%.

(3) La disociación entre el efecto anti-inflamatorio y los demás efectos endocrinos parece más acentuada con la hidrocortisona que con el acetato de cortisona; con dosis más pequeñas pero igualmente eficaces de hidrocortisona se puede evitar o controlar más facilmente la manifestaciones indeseables del exceso hormonal.

(4) Como agente precisando una administración interna prolongada en enfermedades crónicas que responden a su acción, como en la artritis reumatoide, la hidrocortisona parece terapéuticamente superior al acetato de cortisona.

FACTORS IN GOLD DOSAGE AND TOXICITY IN RHEUMATOID ARTHRITIS

BY

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Since the discovery of cortisone, the gold treatment of rheumatoid arthritis has been overshadowed by the dramatic action of this new remedy. As both cortisone and ACTH have been shown to be capable of maintaining their effect in a proportion of cases with appropriate maintenance dosage, and particularly as cortisone can be given by mouth, it would appear at first sight that there can no longer be a place for chrysotherapy in the treatment of this group of disorders. Though this may come to be the position in the future it certainly is not so at present, and until supplies of these newer agents are adequate to serve the needs of all rheumatoid sufferers, gold will continue to be used. It is essential, therefore, that it be used to the greatest advantage and any means by which toxicity can be reduced without impairment of therapeutic benefit must be carefully investigated.

The ability of gold to induce remissions in rheumatoid arthritis has been shown by controlled therapeutic trials (Ellman and Lawrence, 1938a, b; Ellman and others, 1940; Fraser, 1945; Kling and others, 1949), but the high relapse rates (Egelius and others, 1952) show that the effect at least with present therapeutic dosage is not curative, relapse being particularly frequent when low dosage has been used (Short and others, 1948; Browning and others, 1947). Owing to the very slow excretion rate of gold, however, relapses may not occur for some considerable time, and even after an observation period of 9 years patients treated with gold have been found to fare better than those receiving other methods of treatment (Kling and others, 1949). That the effect of gold is proportional to dosage has been shown in animals by Sabin and Warren (1940), and in man by Ellman and others (1940). Some workers have suggested that dosage of the order of 50 mg. weekly may be as effective as a larger dose (Freyberg and others, 1941 ; Comroe, 1945), but they have produced no statistical evidence in support of their claim. The indications from animal experiments are that the optimum total dosage is of the order of 100 mg./kg. (6 g./60 kg.) given over the shortest possible time.

It would appear, therefore, that successful gold treatment depends on administering a maximum dosage of gold whilst at the same time avoiding its more dangerous side-effects. Before discussing how this may best be achieved, it is necessary to consider certain pharmacological properties of gold.

Gold compounds injected intramuscularly are slowly absorbed from the site of injection, attaining, with normal therapeutic dosage, a maximum blood level of up to 2 mg./100 ml. of plasma by the 4th weekly injection. After stopping treatment the blood level slowly falls; reaches half its final level by the 9th week, but still continues to show detectable amounts at the end of the 4th month. Gold can be detected in the urine up to 10 months after stopping treatment (Freyberg and others, 1941; Hartung and others, 1941), and has been discovered in the tissues after periods of up to 3 years. In the blood, gold is combined with the plasma proteins (Freyberg and others, 1944). This gold-protein complex is a chemical compound and does not release gold ions in solution (Libenson, 1945). As colloids and other substances of high molecular weight present in the plasma can pass out of the circulation only through damaged capillaries, they tend to become concentrated at a site of induced inflammation (Menkin, 1936). It follows that gold in its combination with protein will not readily pass into the tissues except at a focus of inflammation. In a patient with active rheumatoid arthritis the gold will thus pass largely into the inflamed synovial tissues, and the concentration in such tissue has, in fact, been found to be some 18 times as great as in, for example, the skin (Bertrand and others, 1948). Thus, so long as there is active exudation into the diseased tissues, the danger of toxic effects in the skin, mucous

membrane, or haemopoietic tissue is likely to be reduced. As the disease process subsides, however, this shunting effect will diminish and the danger of gold deposition in healthy tissues will be liable to increase, which explains the tendency for toxic effects to be greater in those patients who derive the greatest benefit and greater in rheumatoid arthritis than in a resistant disease such as tuberculosis. It would also explain the inverse relationship between the erythrocyte sedimentation rate and gold toxicity noted by Ellman and others (1940), a relationship which is not absolute since toxic effects may arise when the erythrocyte sedimentation rate is still raised (Goldie, 1939; Price and Leichtentritt, 1943). The most serious and persistent manifestations nearly always arise when quiescence has been reached. In Goldie's series, for example, the erythrocyte sedimentation rate was below 10 mm. during the 2 weeks before the onset in eight out of eleven examples of desquamating erythema. In my own experience, though stomatitis and drug rashes frequently arise in patients in whom the erythrocyte sedimentation rate is still high, they are invariably transient. The persistent forms of stomatitis and dermatitis which were at one time such a distressing feature of chrysotherapy do not occur till the disease is almost or wholly quiescent.

Present Experiments

On the basis of these impressions and in view of the importance of giving the maximum tolerated dose, it was decided to treat a series of patients on a new schedule. In this the maximum dose was given from the start and was based on a scale related to the extent and activity of the disease process as measured by the erythrocyte sedimentation rate or preferably to the actual plasma fibrinogen concentration of which the erythrocyte sedimentation rate is an indirect measure. A fractional viscosity method (Lawrence, 1949, 1950) may conveniently be used for estimating the plasma fibrinogen. The corresponding viscosity differences are therefore given in Table I, which also shows the dosage.

Dosage.—The erythrocyte sedimentation rate or plasma fibrinogen is taken at 4-weekly intervals and the subsequent dosage regulated according to the same scale. Thus a female patient with an erythrocyte sedimentation rate of 50 mm. would start with a weekly dose of 200 mg., and this would be continued till the erythrocyte sedimentation rate fell below 25 mm. If, for example, it fell to 20 mm. the dose was reduced to 100 mg. weekly, if to under 15 mm. the dose fell to 50 mg. weekly. If the erythrocyte sedimentation rate rose, the dosage was increased again in accordance with the scale. No fixed limit was placed on total dosage unless this was necessitated by the appearance of toxic symptoms, but treatment was discontinued when the erythrocyte sedimentation rate had remained within normal limits for 2 months. When plasma fibrinogen values were substituted for the erythrocyte sedimentation rate it was found possible to include in the higher dosage group many cases in which the erythrocyte sedimentation rate was proving a fallacious guide to the activity of the disease process and to prolong treatment till recovery was more complete. If the erythrocyte sedimentation rate alone was used, the danger of an increased value due to anaemia had to be borne in mind. In such cases estimation of the plasma fibrinogen is essential.

Toxic Side-Effects.—Table II (opposite) shows the toxic symptoms in ninety patients. Thirty of these were treated on the old schedule and received two courses each of 2·5 g. gold at a weekly dosage of 200 mg., following the customary initial dose of 10, 20, 50, and 100 mg. at weekly intervals. These patients showed frequent toxic effects, and in many the symptoms were severe, stomatitis and extensive dermatitis causing great distress persisting for many months. One patient in this group developed agranulocytosis and purpura and died (Ellman and Lawrence, 1935).

Thirty others received 100 mg. weekly up to a total of 1·5 g. for each of two courses. Toxic effects were less frequent, stomatitis being comparatively rare and dermatitis less frequent. Blood and liver disorders were not encountered in this group. Nevertheless, the stomatitis and dermatitis of patients treated with such dosage may be severe and prolonged and fatal agranulocytosis is not unknown.

In the remaining thirty, the graded dosage-schedule described above was used. The majority of these patients received a dosage of 200 mg. weekly at some part of the treatment, and for some who proved resistant, doses of 300 mg. were used for a time. Nevertheless, there was significantly less stomatitis in this group than in those receiving set courses of gold at a similar weekly dosage. The difference between this group and those receiving the smaller doses is not significant as regards stomatitis, nor are there any significant differences between any of the groups in any other respect, though it should be noted that Group I shows most dermatitis and is the only

TABLE I
GOLD DOSAGE USED IN THIS INVESTIGATION

Fibrinogen		Erythrocyte Sedimentation Rate (mm./hr, Westergren)		Weekly Dosage of Gold Compound (mg.)
Mg. per cent.	Viscosity Difference	Female	Male	
Over 550	Over 25	Over 25	Over 20	200
450-550	20-24	15-24	10-19	100
Under 450	Under 20	15 and under	9 and under	50

TABLE II

RELATIONSHIP OF DOSAGE SCHEDULES TO TOXICITY IN RHEUMATOID ARTHRITIS TREATED WITH SOLGANAL B OLEOSUM

Group	Dosage	Toxic Side-Effects					Total Patients
		Stomatitis	Dermatitis	Agranulocytosis	Jaundice	Grippe aurique	
I	200 mg. weekly for two courses of 2·5 g.	8	8	1	1	1	30
II	100 mg. weekly for two courses of 1·5 g.	1	5	0	0	0	30
III	200-300 mg. weekly till E.S.R. normal; then 50 mg. weekly for 8 weeks ..	4	6	0	0	2	30
III A	Those in III who had an initial dose of 300 mg.	2	1	0	0	2	13
III B	Those in III who had a dose of 100 mg. for the first two injections	2	5	0	0	0	17

group to show agranulocytosis or jaundice. A feature noted in Group III in two instances and in Group I once was a febrile reaction associated with generalized urticaria, erythema, and aggravation of the joint symptoms occurring about the 12th day of treatment. This reaction closely resembles serum sickness and may well be of the nature of an acquired sensitivity to the gold-plasma-protein complex to which reference has already been made. In Group III it occurred only in those receiving a high loading dose and was then of such severity that a lower initial dosage was substituted. Since the initial two doses have been reduced to 100 mg. weekly it has not been encountered.

The data given in Table II can give only a very inadequate indication of the difference between these methods of treatment. The stomatitis and dermatitis encountered in Group III were very different in character from those in Groups I and II. In the latter they were frequently severe and associated with extensive ulceration of the mouth and gums and an eruption involving the face and limbs and sometimes also the trunk, the pain and itching sometimes causing serious loss of sleep. Moreover, both the stomatitis and dermatitis sometimes proved very intractable, the former sometimes lasting for a month or more, the latter for over a year in some instances. In Group III, on the other hand, the lesions of both mouth and skin were mild and transient and when they had subsided the gold treatment could, if necessary, be resumed with a modified dosage. Occasionally in this group a small scaly patch might persist on the arm or leg, but this did not cause discomfort.

Type of Preparation.—A number of preparations of gold have been used for the treatment of rheumatoid arthritis (Table III), but surprisingly little information is available on their relative toxicity. In acute toxicity experiments in animals (Sabin and Warren, 1941) toleration has proved high and has been found to depend less on the proportion of gold in a compound than on the nature of the radical to which the gold is attached and on its solubility. Thus the insoluble gold compounds such as calcium aurothiomalate were found least toxic, a dose of 5 g./kg. being tolerated, whereas only 0·2 g./kg. sodium aurothiomalate could be given. These doses, however, far exceed normal therapeutic doses in man which are of the order of 2 mg./kg. Chronic toxicity experiments in animals which would be much more informative do not appear to have been made.

TABLE III

ORGANIC GOLD COMPOUNDS USED IN TREATMENT

Chemical Name	Proprietary Name
Sodium aurothiosulphate	Sanocrysin, Crisalbine
Sodium aurothiopropanol sulphonate	Allochrysine
Sodium aurothioglucose	Solganal B
Sodium aurothiomalate	Myocrisin
Calcium aurothiomalate	Aurocalcium
Sodium aurothiosinamine benzoic acid	Lopion
Gold-keratin compound	Aurodetoxin

Gold toxicity in patients under treatment with gold was studied by Hartfall and others (1937), who used a number of gold preparations and did not find them all equally toxic. Toxic reactions were more frequent with Myocrisin and Crisalbine, containing 50 and 37 per cent. of gold respectively, than with Solganal and Lopion containing 40 and 50 per cent. respectively, so that toxicity was unrelated to gold content. Severe reactions occurred most frequently with Myocrisin (6 per cent. of 67 cases) and least commonly with Solganal (1·6 per cent. of 301 cases). With all preparations, skin manifestations were more frequent than any other toxic reaction and generally took the form of an erythematous eruption with pruritus. Peripheral neuritis was encountered in two patients, both of whom had been treated with Myocrisin. Stomatitis and jaundice were also relatively more frequent in those having Myocrisin. Purpura occurred in nine of the total of 1,415 patients and agranulocytosis in one, the purpura being equally distributed amongst patients receiving different preparations of gold.

Snorrason (1952) treated patients with Sanocrysin, and serious toxic effects occurred in 6 per cent. Sundelin (1941) administered calcium gluconate at the same time as the gold in a proportion of his

TABLE IV

TOXIC SYMPTOMS ARISING DURING TREATMENT WITH DIFFERENT PREPARATIONS OF GOLD

Preparation	Total Treated	Toxic Side-Effects									
		Stomatitis		Skin Eruption		Albuminuria		Polyneuritis	Purpura	Pruritus	
		No.	%	No.	%	No.	%			No.	%
Sodium aurothiomalate (aqueous)	33	19	63	11	37	5	20	2	0	2	7
Sodium aurothioglucose (oily) ..	25	8	30	8	30	5	20	0	1	2	8
Sodium aurothiomalate (oily) ..	2	0		0		0		0	0	0	
Sodium aurothioglucose (aqueous)	5	3		1		2		0	0	0	
Calcium aurothiomalate	4	3		1		0		0	0	1	

cases, but did not find the incidence of complications reduced.

The writer has, during the past 10 years, administered aurothiomalate (Myocrysin or Aurocalcium) to alternate patients with rheumatoid arthritis, and Solganal B to the remainder. In this way a group of 66 patients has been studied for a sufficient time to assess toxicity. The toxic symptoms are shown in Table IV; these patients were treated according to the schedule already described, in which the dose was greatly reduced when the erythrocyte sedimentation rate or plasma fibrinogen had reached a normal level. With this schedule, as already noted, there were no blood or liver disorders. Myocrisin was administered chiefly in aqueous solution, and Solganal B in a suspension in oil which was, until recently, the only form in which it was available. Since an aqueous solution of Solganal B has come available it has been studied alternately with the oily preparation in the Solganal group, and for comparison an oily suspension of Myocrisin is also now being used in alternate Myocrysin patients. The numbers treated with aqueous Solganal and oily Myocrisin on which data are available are as yet small and will be the subject of a later report, but they are included in the Table. Four patients treated with calcium aurothiomalate (Aurocalcium) are also included.

Results.—The most striking feature of this study is the high incidence of stomatitis in the Myocrisin treated series. Over half the patients had stomatitis at some time during the treatment, compared with only one out of eight receiving Solganal B. Despite the small numbers, this difference is highly significant. Dermatitis also tended to be more frequent in the Myocrisin group, but both in this group and in those receiving Solganal, it rapidly subsided when treatment was stopped, and it was found possible to resume treatment with a modified dosage where such a resumption was required. In a few instances, a small dry, scaly patch remained, generally in the region of the knee or elbow, but by then the disease had generally been controlled and only a low maintenance dosage was thereafter required. Albuminuria was found with similar frequency in those treated with Myocrisin and Solganal B. It was not associated with symptomatology or with laboratory evidence of renal impairment in either group, and, though dosage was modified when this complication arose, it was not found necessary to discontinue treatment. Polyneuritis supervened in two patients treated with Myocrisin. In one of these, who has already been reported (Leiper, 1946), it subsided in the course of the next 3½ months when it was found that the rheumatoid process had been completely suppressed. In the second patient it arose at a time when the value of monthly maintenance doses was being studied. As a monthly dose of 50 mg. had been found inadequate in earlier cases, 100 mg. monthly was used for this patient. The first six of these monthly maintenance doses were given without ill effect, but the seventh was followed by a severe histamine-like reaction, characterized by flushing and loss of consciousness, the pulse becoming imperceptible for about a minute. This was followed a day or two later by weakness of the right leg and both arms which is still present 19 months later. It should be pointed out that in this case a dose of 100 mg. was used at a time when both the erythrocyte sedimentation rate and plasma fibrinogen were within normal limits, so that dosage was excessive according to the schedule already outlined. Histamine-like reactions characterized by flushing, headache, and sometimes unconsciousness with imperceptible pulse, occurred in several patients treated with this batch of Myocrisin, but no others developed polyneuritis or other ill-effects. The samples had turned a dark-brown colour due to exposure to light and showed increased toxicity to chicks, and it was concluded that some highly toxic decomposition-product had been formed from the gold salt. Similar histamine-like reactions have been noted by others with certain batches of Myocrisin (Barber, 1952), and the author had a similar experience with another batch, which had, however, been kept in a hospital dispensary for 6 years.

The purpura which appeared in one patient on

TABLE V

RELATIVE EFFICIENCY OF AUROTHIOGLUCOSE AND AUROTHIOMALATE IN PATIENTS IN WHOM TREATMENT WAS STARTED BEFORE AUGUST, 1951*

Preparation	Weekly Dose	Total Patients	Results					Refused treatment or ceased to attend	Erythrocyte sedimentation rate finally normal in three consecutive monthly tests	
			Quiescent		Improved	No change	Worse			
			No.	%					No.	%
Sodium Aurothioglucose (Solganal B)	200-300 mg.	56	22	39	30	2	0	2	38	68
	100 mg.	30	8	27	20	1	1		11	37
Sodium Aurothiomalate (Myocrisin)	200-300 mg.	27	10	37	16	0	0	1	15	55
Control	Sterile almond oil	30	1	3	22	6	1	0	4	13

* This table includes data from an earlier investigation (Ellman and others, 1940).

Solganal B was unassociated with thrombocytopenia and proved transient. Pruritus was complained of by two patients treated with Myocrisin and by two receiving Solganal. In the former it was limited to the anal region, in the latter it was more generalized. In all it was very transient and caused little inconvenience.

The number of patients treated with oily Myocrisin and aqueous Solganal is small, but it would appear that aqueous Solganal shows the same tendency to produce stomatitis as the aqueous preparation of Myocrisin. The use of Aurocalcium (calcium aurothiomalate) was discontinued after it had been used in four patients, all of whom developed toxic manifestations, three of them stomatitis. This stomatitis differed from that resulting from treatment with other gold preparations in being more widespread and always associated with an eruption on the inside of the cheeks.

Comparative Efficacy.—Diminished toxicity is of practical importance only if associated with undiminished therapeutic efficiency. Data on therapeutic effect are accordingly shown in Table V. In this table all patients on high dosage of Solganal B have been included, whether on the original two-course scheme or on the later schedule, the results by these two methods being closely similar. A group of patients on a lower dosage of Solganal B has also been included. Myocrisin was not studied in the lower dosage or by the two-course scheme. The control group received injections of sterile almond oil once weekly as described in a previous paper (Ellman and others, 1940). Assessment of results was made on completion of treatment or at the end of 9 months.

The term "quiescent" is used to indicate the absence of pain, either spontaneous or on movement of the affected joints, associated with a normal erythrocyte sedimentation rate and plasma fibrinogen. The erythrocyte sedimentation rate, estimated by the Westergren method, was considered normal when below 10 mm. in the male and 16 mm. in the female. A number of patients still complained of slight residual pain after the blood findings had become normal. Some of these showed evidence of osteo-arthritis in the painful joints, but were not labelled as quiescent.

It is clear from the data in Table V that Myocrisin has no greater therapeutic effect than Solganal B. The indications are rather that its effect may be less, fewer attaining a normal erythrocyte sedimentation rate amongst those treated with it, but the differences are not significant and may well be due to more frequent interruption of treatment because of toxicity in this group. Nor is there any significant difference between the Myocrisin group and those receiving small doses of Solganal. There are, of course, highly significant differences between both the Myocrisin and large-dose Solganal group and the controls, and the differences between high-dose Solganal and low-dose Solganal, and between low-dose Solganal and the controls are significant as regards the erythrocyte sedimentation rate.

Data are unfortunately not now available regarding return to work amongst the earlier cases studied, including those in the small-dose Solganal and control groups, but of the later high-dose Solganal and Myocrisin groups, all those below the age of 65 have returned to work, apart from one patient who also had severe disk degeneration.

Discussion

Preparation.—It is clear from all data so far considered that toxicity does not depend on the proportion of gold in the compound used, and some feature in the organic part of the molecule must

therefore be held responsible. On the other hand, the toxic symptoms are those which commonly arise in heavy metal poisoning and are presumably due to the gold ion. This may be explained if it is assumed that the organic fraction determines the distribution in the tissues and eventual disposal. As the excretion of gold is extremely slow, it is unlikely that relative excretion rates play an important part in toxicity, and it seems more probable that distribution in the body is the main factor. The importance of molecular size in determining the relative concentration in diseased tissues has already been noted in this connection, and it is therefore of interest that, whereas Myocrisin, which is more toxic, has a molecular weight of 390, the molecular weight of Solganal B is, by virtue of a certain degree of polymerization, of the order of 1,000. The fact that the Solganal used for the greater part of these trials was in an oily suspension and the Myocrisin was in aqueous solution may have played a part. If, for example, a higher peak blood level were attained after injection of an aqueous solution, the combining-power of the plasma proteins for gold might be exceeded and permit of greater diffusion of the gold through undamaged capillaries into tissues other than those of the diseased joints.

An important point which arises from this study is that total dosage of gold is not important. One patient in this series had as much as 9 g. without a pause, and apart from a transient pruritus and gingivitis, suffered no ill-effect. Though gold must undoubtedly accumulate in the tissues, it would appear to become fixed and to be no longer capable of producing toxic effects, though rarely a toxic effect on the blood-forming organs has been known to arise some time after treatment, possibly due to reactivation of gold fixed in the tissues.

Duration of Treatment.—A decision as to the duration of treatment must depend on whether gold therapy is regarded as curative or suppressive. It is well recognized that relapses are frequent in patients treated with gold, though they may not occur for some considerable time after the cessation of treatment, particularly if high dosage has been used. As, however, the excretion of gold is very slow and may not be complete after 3 years, a suppressive action is not ruled out. It is indeed supported in some measure by the differential agglutination test, whose titre is not at once reduced by successful aurotherapy, and may be higher when the disease has reached the quiescent stage than before starting treatment. In this respect gold resembles cortisone, which is also without effect on the differential agglutination test. Moreover, in arthritis of known aetiology, as, for example, the infective arthritis of rats, which histologically shows a close resemblance to rheumatoid arthritis, the causative virus has not been found susceptible, though the disease process can be completely suppressed by aurotherapy (Sabin and Warren, 1940).

If aurotherapy is merely suppressive, it would seem reasonable to provide some sort of maintenance treatment once the quiescent stage has been reached. This poses a difficult problem, and two alternative solutions are at present being studied:

(*i*) To give maintenance doses of, say, 50 mg. every 4th week for a prolonged period, until, for example, all signs of activity have been absent for 3 years. A longer period may, of course, prove to be necessary, and the differential agglutination test, if it is indeed an index of the continued presence of the aetiological agent, may assist in this respect. Even on such a maintenance dosage, the condition may recur, as happened in one patient in the present series. If this should happen the dosage should not be increased unless the plasma fibrinogen content rises, but the injections may be given more frequently.

(*ii*) To keep the patient under observation without maintenance dosage of gold, the erythrocyte sedimentation rate and plasma fibrinogen being taken at intervals of 3 to 6 months. If evidence of relapse appears the treatment may then be resumed.

It is too soon at present to say which of these alternatives should be preferred. The danger of relapse is probably greater when treatment is interrupted, as patients on this routine are more likely to stop attending, and may not reappear till the relapse is in an advanced stage. This must be placed against the possibility of toxic effects arising from maintenance dosage, if the former alternative is adopted.

Summary

Alternate patients on gold therapy for rheumatoid arthritis received aurothioglucose (Solganal B oleosum) and aurothiomalate (Myocrisin or Aurocalcium).

The aurothioglucose proved significantly less toxic, the incidence of stomatitis being halved. Polyneuritis occurred in two patients receiving aurothiomalate, but in none of those treated with aurothioglucose. The possible factors responsible for this difference in toxicity are discussed.

No significant difference in therapeutic efficiency was found between these two compounds.

A method is described whereby the greater therapeutic efficiency of a high dosage (up to 200 mg. weekly) of gold in rheumatoid arthritis may be attained without the greater incidence of side-effects

normally present with such a dose. The method depends on an adjustment of gold dosage in relation to the activity of the disease process as determined by the fibrinogen content of the plasma.

In a series of 66 patients treated in this way, no blood dyscrasias or chronic skin eruptions were encountered, and all those under the age of 65 were able to return to work. The blood sedimentation rate was maintained at a normal level in 57 per cent. of patients treated on this schedule as compared with 37 per cent. of patients receiving a standard dosage of 100 mg. weekly. Only two (4 per cent.) failed to improve.

I wish to thank Messrs Schering for supplies of Solganal B aquosum for use in this trial, and Messrs May and Baker for kindly carrying out toxicity tests on a sample of Myocrisin.

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Facteurs posologiques et toxiques de la chrysothérapie de l'arthrite rhumatismale

RÉSUMÉ

Au cours de la chrysothérapie de l'arthrite rhumatismale les malades alternatifs ont reçu de l'aurothioglucose (Solganal B oleosum) et les autres de l'aurothiomalate (Myocrisine ou Aurocalcium).

L'aurothioglucose s'est montrée clairement moins toxique, réduisant de moitié la fréquence de la stomatite. La polynévrite survint chez deux malades traités par l'aurothiomalate, sans apparaître chez ceux traités par l'aurothioglucose. On discute les facteurs pouvant expliquer cette différence de toxicité.

On n'a pas trouvé de nette différence entre ces deux produits en ce qui concerne leur efficacité thérapeutique.

On décrit une méthode qui dans l'arthrite rhumatismale augmente l'efficacité thérapeutique grâce à l'emploi de fortes doses (jusqu'à 200 mg. par semaine) sans augmenter la fréquence des incidents secondaires que de telles doses entrainent généralement. D'après cette méthode on ajuste les doses des sels d'or en fonction de l'activité morbide indiquée par le taux sanguin du fibrinogène.

Dans un groupe de 66 malades ainsi traités on n'a pas observé de dyscrasie sanguine ou d'exanthème et tous les maldes âgés de moins de 65 ans ont pu reprendre leur travail. La vitesse de la sédimentation globulaire s'est maintenu normale chez 57% des malades traités par cette méthode et chez 37% seulement de ceux traités par des doses habituelles de 100 mg. par semaine. Deux malades seulement (4%) n'accusèrent pas d'amélioration.

Factores posológicos y tóxicos en la auroterapia de la artritis reumatoide

SUMARIO

En el curso de la crisoterapia de la artritis reumatoide los enfermos alternativos fueron tratados con aurotioglucosa (Solganal B oleosum) y los demás con aurotiomalato (Myocrisin o Aurocalcium).

La aurotioglucosa resultó ser netamente menos tóxica, reduciendo de la mitad la incidencia de estomatitis. La polineuritis sobrevino en dos enfermos tratados con el aurotiomalato sin aparecer en los tratados con aurotioglucosa. Se discute los factores probables que motivan esta diferencia de toxicidad.

No se encontró diferencia significante en la eficacia terapéutica de los dos productos.

Se describe un método de tratamiento de la artritis reumatoide que permite aumentar su eficacia con altas dosis (hasta 200 mg. semanales) de oro sin aumentar la incidencia de efectos secundarios, habituales con tales dosis. Este método consiste en un ajuste de las dosis de sales de oro en relación a la actividad morbosa reflejada en la tasa de fibrinógeno en el plasma.

En un grupo de 66 enfermos así tratados no hubo discrasia sanguinea ni exantema y todos los enfermos de menos de 65 años de edad pudieron volver a su trabajo. La velocidad de sedimentación globular mantúvose normal en el 57% de los enfermos tratados con este método y tan sólo en el 37% de los tratados con dosis habituales de 100 mg. por semana. Dos enfermos solamente (4%) no acusaron mejoría alguna.

H.P.C. (3-HYDROXY-2-PHENYLCINCHONINIC ACID) IN RHEUMATOID ARTHRITIS*

BY

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Since the discovery of the anti-rheumatic effects of ACTH and cortisone by Hench, Kendall, Slocumb, and Polley (1949), many attempts have been made to find compounds which may have a similar action. In the investigation of the pharmacological properties of certain cinchoninic acid derivatives, Blanchard and others (1950a) found that the compound 3-hydroxy-2-phenylcinchoninic acid (H.P.C.) decreased the adrenal ascorbic acid content of the intact rat, but not of the hypophysectomized rat. They therefore suggested that H.P.C. might be effective in diseases which respond to ACTH, and reported a clinical trial in which the compound was given to ten patients with acute rheumatic fever, ten with chronic rheumatoid arthritis, three with bronchial asthma, and two with disseminated lupus erythematosus (Blanchard and others, 1950b). Fever, malaise, and arthritis were rapidly controlled in rheumatic fever, but in rheumatoid arthritis, although most patients improved subjectively, only two showed any objective change. The drug was administered orally, the dose being 10 to 20 mg./kg. body weight daily or on alternate days for periods up to 21 days.

The response to the compound in rheumatic fever was confirmed by Rennie and others (1951), who also found striking improvement in three patients suffering from scleroderma. The dose used was 20 mg./kg. body weight daily, increasing to 40 mg. for 1 to 3 weeks.

Using a similar dose, Simson and Bunim (1951) reported marked improvement in six cases of rheumatic fever and also in four cases of gout. Of ten patients with rheumatoid arthritis, seven improved to a degree comparable to that obtained with salicylates, but not to that obtained with cortisone or ACTH. One or more toxic reactions occurred in six of the twenty patients treated, but in only four of these were the undesirable effects severe enough to necessitate interruption of therapy.

Toxic effects were also reported by Jager (1952) in the treatment of 35 cases suffering from one of the so-called collagen disorders. The most common toxic manifestations were skin eruptions (13 patients) and diarrhoea (eight patients). The daily dose ranged from 15 to 50 mg./kg. body weight for periods varying from less than 1 month to 16 months. Of the 35 patients treated, 21 were suffering from rheumatoid arthritis. Although joint discomfort was relieved, the drug did not appear to alter the course of the disease, nor did it have any effect on the usual laboratory tests.

Present Investigations

In view of these promising reports, it was decided to conduct a controlled therapeutic trial of H.P.C. to evaluate its use in active rheumatoid arthritis.† In the first instance, a pilot series of 21 cases was investigated and in these control tablets were given for a period and followed by the agent under trial. Subsequently, in another series of cases, 51 patients were given either H.P.C. or control tablets, the order of administration being selected at random. In both series, the identity of the inert substance and the agent under trial was, as far as possible, unknown to both patient and observer.

All the patients were suffering from active rheumatoid arthritis, and were initially treated in hospital with rest splints, remedial exercises, and physiotherapy for 2 weeks before the administration of the tablets was begun. Patients who were subsequently given maintenance therapy took the tablets after discharge from hospital and were seen at a special follow-up out-patient clinic.

Patients were assessed twice weekly whilst in hospital. Those receiving maintenance treatment were assessed as out-patients, after one month and after 3 months of such treatment. The assessment

* Read to the Heberden Society on December 13, 1952.

† The drug was provided in the form of yellow tablets, each containing 200 mg. for oral administration, by Messrs. May and Baker, who also supplied control tablets containing lactose, which were identical in appearance.

was essentially clinical, attention being paid to general feeling of well-being, spontaneous pain (including rest pain), stiffness, joint tenderness, swelling, and range of movement, in addition to functional ability as indicated by the familiar and accustomed movements of everyday life. At all assessments, patients were weighed. Estimations of the erythrocyte sedimentation rate and haemoglobin level were done before and immediately after treatment in hospital, and at the time of all out-patient follow-up assessments.

Pilot Series.—The 21 patients in the pilot series were given control tablets for periods varying from 2 to 21 days (average 10 days), and were then all transferred (unknown to both patient and observer) to the H.P.C. tablets, which were continued for 10 to 36 days (average 20 days). The control tablets were always administered in exactly the same way as the H.P.C. tablets that followed. In all cases the initial dose of the drug was 1·2 g. (six tablets) daily, this being equivalent to 20 mg./kg. of an average body weight of 60 kg. (132 lb.). In order to reduce toxic effects to a minimum, the total daily dose was divided into three, taken in milk at hourly intervals, the first dose being taken after breakfast. The initial dose was continued until the patient either improved clinically or developed toxic symptoms. If neither change occurred after a week, the dose was increased to a maximum of 2·4 g. daily. In some cases, the dose was reduced to 0·6 g. daily because of toxic symptoms. In this way, an attempt was made to determine the optimum dose which would produce the maximal clinical benefit with minimal complications. This was found to be 1·2 g. daily.

The clinical results of the pilot series are shown in Table I, which demonstrates maximum clinical change. It can be seen that twenty patients improved on H.P.C. (fifteen markedly) compared with only twelve on control tablets (none markedly). Only one patient's condition was unchanged with the drug, whereas nine patients in the control group either showed no change or deteriorated. Analysis of the figures by the χ^2 test shows that there is a marked statistically significant difference between treated and control, p being less than 0·01.

TABLE I

MAXIMUM CLINICAL CHANGES IN PILOT SERIES OF 21 PATIENTS

Degree of Clinical Change	Therapy	
	H.P.C.	Control
Much Improvement	15	0
Slight Improvement	5	12
No Change	1	2
Deterioration	0	7
Total Cases Tested	21	21

Random Selected Series.—Encouraged by this experience, a second series of cases, controlled by random sampling, was investigated. 51 patients were treated either with H.P.C. or with the control. H.P.C. was given to 26 patients and the control tablets to 25. The dose of the former was standardized at 1·2 g. daily. This was continued for 21 days, the method of administration being the same as that employed in the pilot series. If, during this period, toxic symptoms developed with the H.P.C. either the drug was stopped or the dose was reduced to 0·6 g. daily. At the end of the period, all patients in each group who showed marked improvement without toxic effects, took a maintenance dose of four tablets daily for 3 months. Such maintenance therapy was given to six patients taking control tablets and to eleven patients treated with H.P.C.

The clinical changes observed after 21 days treatment are shown in Table II. Although the proportion of "much improved" cases was greater with H.P.C. than with the control, statistical analysis of the figures shows that the difference between the treated and control groups may have occurred by chance, and is therefore not significant ($0·30 > p > 0·20$).

TABLE II

CLINICAL CHANGES AFTER 21 DAYS IN RANDOM SELECTED SERIES OF 51 PATIENTS

Degree of Clinical Change	Therapy	
	H.P.C.	Control
Much Improvement	14	9
Slight Improvement	9	9
No Change	3	3
Deterioration	0	4
Total Cases Tested	26	25

Of the eleven patients who continued with H.P.C. in maintenance doses, six retained their improvement after 3 months. None of the six control patients on maintenance therapy deteriorated after a similar period.

Sedimentation rates and haemoglobin levels were not significantly changed in either control or treated groups, nor was there any appreciable change in weight.

Toxic Complications

The most common toxic effects of H.P.C. were gastro-intestinal symptoms and skin eruptions. Neither of these disturbances occurred in patients taking control tablets.

Gastro-Intestinal Symptoms.—These included nausea, abdominal pain, and diarrhoea. They varied

in severity from mild nausea with a feeling of abdominal discomfort to marked diarrhoea with colicky abdominal pains associated with general malaise and fever. In mild cases, the symptoms disappeared with the continued use of H.P.C. either spontaneously or with small doses of Mist. Kaolin B.P.C. The most severe symptoms usually occurred when the dose was increased to 2·4 g. daily, and the drug had then to be discontinued in six out of nine patients who were taking this larger dose. Withdrawal of the drug because of troublesome diarrhoea was also necessary in seven out of 38 cases taking 1·2 g. daily. There were no gastro-intestinal disturbances with doses of 0·6 g. and 0·8 g. daily, although the latter was continued as maintenance therapy for 3 months. The onset of toxic effects did not necessarily coincide with maximal clinical improvement as is so frequently the case with aurotherapy.

Skin Eruptions.—Of the 21 cases in the pilot series, seven developed skin rashes. These were urticarial in nature, suggesting drug sensitivity, and they responded well to systemic and local antihistamine drugs. The eruptions developed on the exposed parts (particularly hands and face) and usually appeared on going into the open air, especially on exposure to sunlight. The drug was first used during the summer of 1951 when these skin reactions were first noticed. The random selected series was started in the autumn of 1951 and continued throughout the winter and into the summer of 1952. During the winter, skin reactions did not occur. When the summer weather began, however, the eruptions were again encountered, especially in those patients on maintenance therapy. Out of the eleven cases, nine developed skin rashes at some time during the 3 months' treatment. The eruptions again developed on the exposed parts, but often extended to the scalp, neck, and arms. They differed from those occurring in the previous summer in that they were chiefly vesicular, but erythematous and scaling forms were also seen. These skin rashes were often quite troublesome, the vesicular type becoming crusted, and the drug had to be stopped in three cases. As in the case of the gastro-intestinal toxic symptoms, there appeared to be no correlation between maximal clinical improvement and the onset of skin eruptions, nor was there any correlation between the two groups of toxic complications.

In view of the clinical evidence of photosensitivity in the pilot series, skin sensitivity tests were performed before, during, and immediately after the course of treatment in hospital in the random selected series. For this purpose an Alpine Sun Hanovia lamp was used at a distance of 36 in. for half a minute and one minute, to a localized area of normally unexposed skin (abdomen). There was complete lack of correlation between the development of skin eruptions and the response to ultra-violet irradiation. During the winter months, several patients became more sensitive to artificial sunlight during the course of treatment and yet developed no rash. On the other hand, none of the patients who developed severe vesicular and erythematous eruptions showed any increased response to ultra-violet light from the artificial source.

Summary and Conclusions

In a pilot series of 21 cases, the patients were all given control tablets for periods of 2 to 21 (average 10) days and were then all transferred to H.P.C. tablets for 10 to 36 (average 20) days. Twenty of these patients showed improvement during the H.P.C. therapy, whereas only twelve had shown slight improvement while taking the control tablets.

In a second series of 51 cases, 26 patients were given 1·2 g. H.P.C. daily, and 25 received control tablets. Fourteen treated cases and nine controls were much improved after 21 days, a proportion that could not have occurred by chance.

The excellent results in the pilot series are probably misleading, as these patients were all given the control tablets before the drug, which was then continued for a longer period. It is thus considered that the results of the second random selected series provide a more reliable and accurate evaluation of the efficacy of H.P.C. Although the proportion of patients in the second series who improved during H.P.C. therapy is greater than that of those who improved with the control tablets, the difference is not significant. The beneficial effect of H.P.C. in rheumatoid arthritis has thus not been conclusively proven.

Furthermore, the toxic effects of the drug cannot be minimized as they occurred in a high proportion of cases and were often sufficiently severe to necessitate withdrawal of therapy: 55 per cent. of patients taking 1·2 g. daily developed some gastro-intestinal symptoms, and in one-third of these, the drug had to be discontinued; skin eruptions of varying severity developed in nine out of eleven patients taking the drug for 3 months, and treatment had to be stopped in three. No relation between toxic effects and clinical improvement was noted.

We are indebted to Dr. R. Thrower, of Messrs. May and Baker, for the supply of H.P.C. and control tablets. We would also like to thank Miss E. A. Worsp for carrying out the skin sensitivity tests.

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H.P.C. (Acide 3-hydroxy-2 phényl cinchoninique) dans l'arthrite rhumatismale

RÉSUMÉ

Dans une série préliminaire de 21 cas, tous les malades reçurent pendant 2 à 21 (10 en moyenne) jours des comprimés inertes, suivis pendant 10 à 36 (20 en moyenne) jours de comprimés de H.P.C. Vingt de ces malades accusèrent une amélioration lors du traitement par l'H.P.C., tandis que douze seulement montrèrent une légère amélioration lors du traitement par les comprimés-témoins.

Dans la deuxième série de 51 cas, 26 malades reçurent 1,2 g. d'H.P.C. par jour et 25 malades reçurent des comprimés inertes. Au bout de 21 jours, 14 cas traités et 9 témoins furent tres améliorés—une proportion qui pourrait être due au hasard.

Les excellents résultats dans la première série sont probablement fallacieux, car ces malades reçurent les comprimés inertes avant de recevoir le médicament, lequel fut ensuite administré pendant une période plus longue.

On considère donc que les résultats de la seconde série des cas pris au hasard permettent une évaluation plus sure et plus précise de l'efficacité de l'H.P.C. Bien que dans la seconde série le nombre des malades améliorés après l'H.P.C. soit supérieur à celui des malades témoins améliorés, la différence n'est pas signifiante. L'effet favorable de l'H.P.C. dans l'arthrite rhumatismale n'est donc pas irréfutablement prouvé.

De plus, il ne faut pas négliger les effets toxiques de ce médicament: ils survinrent dans un grand nombre des cas et furent souvent si graves qu'il fallut interrompre le traitement; 55% des malades prenant 1,2 mg. par jour manifestèrent des symptômes gastro-intestinaux et chez un tiers d'entre eux il fut nécessaire d'interrompre le traitement; des exanthèmes de sévérité variable apparurent chez 9 sur 11 malades prenant ce médicament pendant 3 mois et il fallut cesser le traitement chez 3 d'entre eux. On ne nota aucun rapport entre les effets toxiques et l'amélioration clinique.

H.P.C. (Acido 3-hidroxi-2-feni cinconínico) en la artritis reumatoide

SUMARIO

En la serie preliminar de 21 casos, todos los enfermos recibieron durante 2 a 21 (10 promedio) días comprimidos de control, seguidos durante 10 a 36 (20 promedio) días de comprimidos de H.P.C. Veinte de estos enfermos acusaron una mejoría durante el tratamiento por el H.P.C., mientras que doce de ellos solamente mostraron una ligera mejoría con los comprimidos de control.

En la segunda serie de 51 casos, 26 enfermos recibieron 1,2 g. de H.P.C. por día y 25 enfermos recibieron comprimidos de control. Al cabo de 21 días, 14 casos tratados y 9 controles acusaron mejoría—una proporción que podría deberse a la casualidad.

Los excelentes resultados en la primera series fueron probablemente delusorios, ya que estos enfermos recibieron los comprimidos de control antes de recibir el producto que fué luego administrado durante un período más prolongado.

Se considera, pués, que los resultados de la segunda serie de casos casualmente escogidos permiten una valoración más segura y más exacta de la eficacia del H.P.C. Aunque en la segunda serie el número de los enfermos mejorados con el H.P.C. sea superior al de los testigos majorados, la diferencia no es significante. El efecto beneficioso del H.P.C. en la artritis reumatoide no está, pués, conclusivamente probado.

Además, no se puede menospreciar los efectos tóxicos del producto: éstos ocurrieron en un gran número de los casos y fueron a menudo bastante graves para cesar el tratamiento; 55 por ciento de los enfermos tomando 1,2 mg. diarios manifestaron síntomas gastro-intestinales y en una tercera parte de ellos hubo que interrumpir la medicación; exantemas de severidad variable aparecieron en 9 sobre 11 enfermos tratados durante 3 meses necesitando la cesación de la cura en tres. No se halló relación alguna entre los efectos tóxicos y la mejoría clínica.

CORTISONE AND HEPARIN

BY

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(RECEIVED FOR PUBLICATION FEBRUARY 25, 1953)

Though the abundant data published in the literature concerning the influence of cortisone on the thrombo-plastic powers of the blood is varied and sometimes even contradictory, we have concentrated our attention on the eventual influence of cortisone on heparin, the main factor of the circulating anti-coagulating substances. This decision was taken in consideration of the supposed existence of correlations between heparin, hyaluronic acid, and the enzymes of collagenasic, hyaluronidasic types, etc., of connective tissues.

In fifteen patients of different age and sex, received at the Institute of Medical Semiology of the University of Rome, who were affected with evolutive rheumatoid arthritis, we performed the "heparin tolerance test" during a period of therapeutical rest of at least 5 days. This was the test proposed by De Takats (1943) and De Takats and Gilbert (1943) to check the heparin reactivity in individuals who had to be submitted to anti-coagulating therapy.

Technique

After having checked the coagulation time (C.T.) of the patient's blood *in toto*, we made an intravenous injection of 50 mg. heparin exactly measured (instead of the 10 mg. indicated in the original method of De Takats), and again measured the C.T. after 15, 30, 45, and 60 minutes. De Takats classified the different individuals as hypo-reactive, normo-reactive, and hyper-reactive. There was some criticism of this test, but this did not lessen its practical and theoretical value (Menghini and Costantini, 1950). The test was praised by Marmont and Palmieri (1949, 1951) as being sensitive, sure, and simple.

We used Burker's method in determining the C.T., as this is judged one of the most exact. Its method and application were described by Ferrio (1948).

Results

In our fifteen cases of rheumatoid arthritis, the heparin tolerance test gave constant results, the curves being almost identical with those of healthy normal individuals. But the average curve traced after treatment with cortisone, applied for 5 days with a daily dosage of 50-150 mg., shows a markedly flattened trend, expressing a state of hyporeactivity to heparin. Our investigations also showed that cortisone causes great changes in heparin tolerance, and brings about a constant hyporeaction.

Discussion

This part of our results is confirmed by the clinical observations, already published in many countries, of the appearance of blood hyper-coagulability during treatment with ACTH or cortisone.

Our clinical investigations have made a fresh contribution to the complicated problem of the relationship between heparin, hyaluronidase activity, and adrenocortical therapy.

The fact that cortisone appears to cause hyporeaction to heparin may be ascribed to an increase of substances capable of inactivating or neutralizing heparin, of the type of thromboplastin and thrombin. Such an increase could, in theory, easily be ascribed to cortisone, as this substance shows the power of enhancing blood coagulability (see the thromboembolic incidents referred to). The possibility that the diminished tolerance is equal to an increased need of heparin, as we observed after cortisone administration, cannot be rejected; it may be ascribed to a greater consumption or neutralization of heparin. A third, and perhaps better, theory must also be kept in mind, *i.e.* a reduction in the formation of heparin is caused by the number reduction of the mast-cells and their morphologic and histochemical alterations (Asbøe-Hansen, 1950; Cavallero and Sala, 1950).

Even if the interpretation of this problem appears extremely complicated, every new piece of research into the nature and effects of cortisone is interesting.

Summary

The influence of cortisone on heparin, the main factor of the circulating anti-coagulating substances, was studied in fifteen cases of rheumatoid arthritis.

The coagulation time was measured before, and 15, 30, 45, and 60 minutes after, an intravenous injection of 50 mg. heparin; this was done first during a period of therapeutical rest, and then after 5 days' treatment with cortisone (daily dosage 50-150 mg.).

The reaction to heparin was much less after the course of cortisone in every case. The reasons for this hyporeaction are discussed.

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Cortisone et héparine

RÉSUMÉ

Dans quinze cas d'arthrite rhumatismale on étudia l'influence de la cortisone sur l'héparine, facteur anticoagulant principal du sang circulant.

Le temps de coagulation fut déterminé avant, ainsi que 15, 30, 45 et 60 minutes après une injection intraveineuse de 50 mg. de héparine. Ce procédé fut appliqué une fois pendant le repos thérapeutique et répété après une cure de 5 jours de cortisone (50 à 150 mg. par jour).

Dans tous les cas la réaction à la héparine fut diminuée après le traitement par la cortisone. On discute les raisons de cette hyporéaction.

Cortisona y heparina

SUMARIO

La influencia de la cortisona sobre la heparina, factor principal de las substancias anticoagulantes del riego sanguíneo, fué estudiada en quince casos de artritis reumatoide.

El tiempo de coagulación fué medido antes, así como 15, 30, 45 y 60 minutos después de una inyección endovenosa de 50 mg. de heparina, aplicándo este procedimiento durante un período de reposo terapéutico y repitiéndole al cabo de una cura de cinco días de cortisona (50 a 150 mg. diarios).

En todos los casos hubo una disminución de la reacción a la heparina después del tratamiento con la cortisona. Se discuten las razones de esta hiporreacción.

FATAL COMPLICATION FOLLOWING INSULIN THERAPY IN RHEUMATOID ARTHRITIS

BY

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In this hospital, over fifty cases of rheumatoid arthritis have been treated with insulin, as first reported by Kersley and others (1950). In their series, the occurrence of spontaneous hypoglycaemia in two cases shortly after cessation of treatment was the only complication reported (Kersley and others, 1951). Our series has also been free of all major complications with the exception of the one case here described.

Case Report

A fishmonger, aged 71, was first seen in July, 1951, when he complained of pain and stiffness of all the limb joints and the neck for the past 8 weeks. He had also lost 1 st. in weight.

History.—He had suffered from haematemesis in 1949, with recovery on medical treatment. Examination showed the changes typical of rheumatoid arthritis, and the erythrocyte sedimentation rate was 19 mm./hr (Wintrobe). Symptomatic physiotherapy was given, but after 6 weeks he became worse and was admitted to hospital.

On admission, moderate rheumatoid arthritic changes were found in all limb joints, with pain and limitation of movement. The loss of weight was now 2 st. Other systems appeared normal and the urine was clear at all times.

Blood count (September 11, 1951): Hb 59 per cent., R.B.C. 3·2 million/c.mm.; erythrocyte sedimentation rate 47 mm./hr (Wintrobe).

Therapy.—Soluble insulin, 60 units daily, increased after 3 days to 70 units daily, was administered for 5 days in each week for a total of 3 weeks. Hypoglycaemia was stopped after 2½ hrs by oral glucose and a normal breakfast. On no occasion did intravenous glucose prove necessary. Full physiotherapy was also given during this stay in hospital. He showed considerable improvement and was discharged after a further 2 weeks' physiotherapy, walking well.

Relapse.—Two months later his condition had relapsed, and, on December 19, 1951, the erythrocyte sedimentation rate was 54 mm./hr (Wintrobe), and Hb 69 per cent.

Re-admission.—He was re-admitted to hospital on January 14, 1952, and, by this time, was unable to walk, all joints being severely affected. Erythrocyte sedimentation rate was 49 mm./hr (Wintrobe), Hb 59 per cent. Urine normal on routine examination.

Therapy.—A course of soluble insulin was given, as before, for 2 weeks. Again, on no occasion was intravenous glucose necessary. Full physiotherapy was also given during this time. On January 19, 1952, he had a manipulation of shoulders, neck and knees under pentothal anaesthesia. Insulin treatment was stopped on January 25 for the usual weekly interval of 2 days without treatment.

Further Developments.—Thirty-six hours after this last dose of insulin, the patient told his wife he was thirsty, but did not inform us. He had never before complained of excessive thirst. The following noon, twenty hours later, he felt unwell, but no abnormal signs were found. He started to vomit at 8 p.m. on January 27, 1952; at 10 p.m. he was drowsy, the smell of acetone was noticeable in his breath, and no urine had been passed since the vomiting started. At 11.30 p.m. he was catheterized, and the urine was found to contain sugar +++ and acetone +++. A diagnosis of diabetic coma was then made, and treatment started.

Intravenous soluble insulin 300 units, and subcutaneous soluble insulin 280 units was given immediately, and a saline transfusion commenced; 6 hrs later (6 a.m.) another 200 units insulin were given, and 4 hrs later (10 a.m.) another 200 units. The urine test remained orange with Benedict's.

From 12 noon on January 28 further intensive treatment was given (see Table), but the patient died at 5.20 a.m. the following day.

Post-mortem Examination.—Marked cerebral oedema was found, together with oedema of all connective tissues, with moderate pulmonary oedema. Apart from this, no abnormality was detected. Histology of the pancreas, adrenals, and pituitary proved normal.

TABLE

INTENSIVE TREATMENT IN THE LAST HOURS OF LIFE

Time	Soluble Insulin (units)	Other Treatment	Urine Tests	
			Sugar	Acetone
12 noon	400 subcutaneous	2nd litre saline started	Orange	
2 p.m.	400 subcutaneous		Orange	+
3 p.m.	400 subcutaneous	Blood sugar 1.1,000 mg. per cent.	Red	+++
5 p.m.	400 intravenous		Red	+++
6 p.m.	400 intravenous		Red	+++
11 p.m.	1.1,000 intravenous	Saline completed	Orange	+++
12 midnight	1.1,000 intravenous	5 per cent. dextrose started	Red	
1 a.m.	1.1,000 intravenous		Red	
2 a.m.	1.1,000 intravenous		Orange	
3 a.m.	1.1,000 intravenous		Orange	Insufficient urine
4 a.m.		Serum urea 200 mg. per cent.	Orange	
5 a.m.		2nd litre dextrose started		
5.20 a.m.	Patient died			

Comment

This patient appeared to die in an insulin resistant diabetic coma, 8,000 units of insulin in 30 hrs having had no effect. It would appear unlikely that a diabetes of this type would be due to the production of ACTH by insulin therapy, and coma due to depression of endogenous insulin production should have reacted to the large doses of insulin administered.

We cannot find any record of a similar case in the literature, although such a complication might be expected to have occurred in view of the large number of psychiatric patients who have been given insulin therapy.

Summary

A case is reported of a patient who died in an insulin resistant diabetic coma after two courses of insulin therapy for rheumatoid arthritis. Cerebral and pulmonary oedema and oedema of the connective tissue were found *post mortem*.

It is a pleasure to record our thanks to Dr. G. D. Kersley and Dr. J. B. Walker for helpful advice, to Dr. N. E. Rankin and Dr. W. Brumfitt for the pathological investigations, and to Professor Newcombe for his opinion on the histology of the pituitary.

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Complication mortelle de la thérapie insulinique de l'arthrite rhumatismale

RÉSUMÉ

On relate le cas d'un malade mort d'un coma diabétique résistant à l'insuline, survenu après deux séries de thérapie insulinique instituée pour traiter son arthrite rhumatismale. A l'autopsie on trouva de l'oedème du cerveau, du poumon et des tissus conjonctifs.

Complicación letal de la terapia insulínica de la artritis reumatoide

SUMARIO

Se relata el caso de un enfermo muerto de coma diabético resistente a la insulina; el coma sobrevino después de dos curas de insulina al tratar su artritis reumatoide. La necropsia reveló un edema cerebral, pulmonar y de los tejidos conjuntivos.

NEPHROTIC SYNDROME FOLLOWING SODIUM BISMUTH TARTRATE THERAPY IN RHEUMATOID ARTHRITIS

BY

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(RECEIVED FOR PUBLICATION JANUARY 9, 1953)

Parenteral therapy with sodium bismuth tartrate has now been undertaken in rheumatoid arthritis for some time. This salt, according to Martindale (Vol. 2, 1943), is a white powder or yellowish scale preparation containing 35-42 per cent. bismuth. Its general safety can be deduced from the report of Goodman (1948) that almost $\frac{1}{4}$ ton, representing more than $1\frac{1}{2}$ million adult doses, had been administered in the Gold Coast between 1933 and 1942 with no recorded fatalities. The following case is considered worthy of report as an example of fatal renal damage caused by the drug, which was administered in the usual therapeutic dosage.

Case Report

A housewife, aged 39, was seen at the out-patient department of another hospital on March 9, 1949, complaining of recurrent pain and swelling of the hands, elbows, shoulders, feet, knees, and neck of 4 to 5 months' duration. She also complained of weakness, fatigue, and listlessness. Examination showed that her general condition was fairly good, but she was rather anaemic. The affected joints showed the changes of rheumatoid arthritis; there was some fluid in both knee joints. No other abnormalities were noted. Blood count showed a normochromic anaemia (Table). The erythrocyte sedimentation rate (Wintrobe) was 55 mm./1 hr. A catheter specimen of urine showed a trace of albumin, a deposit containing 15-20 pus cells, and an occasional red cell per high-power microscopic field, but no casts or crystals.

On July 14, after a long course of physiotherapy, the first injection of sodium bismuth tartrate 0·5 gr. in 0·5 ml. was given, and she received four further fortnightly injections, the last apparently on September 9. The joints improved slowly, but stiffness was noted for 24 to 48 hours after the injections. On September 28, she reported

TABLE

PATHOLOGICAL DATA

Date	Red Cells (Mil./c.mm.)	Haemoglobin %	White Cells (c.mm.)	Packed Cell Volume (ml.)	Erythrocyte Sedimentation Rate (Wintrobe mm./hr)	Blood Urea (mg./100 ml.)	Plasma Protein (g./100 ml.)	Urine	
								Albuminuria	Microscopy (high-power field)
9/3/49	3·60	72	5,500	35	55			Trace	15-20 pus cells and odd red cell; no casts or crystals.
28/9/49								+++	10-12 pus cells, odd red cell; a few hyaline casts*
9/12/49	4·10	80	9,200				4	+++	Numerous granular and hyaline casts; 3-5 pus cells.
15/12/49						46	3·9 {A=1·5 G=2·4		
30/12/49		86				30		+++	Innumerable granular casts and pus cells.
3/1/50		94					3·5 {A=1·7 G=1·8		
10/1/50						38			
27/6/50	2·40	47	9,000	21	74	170		++++	Numerous hyaline and granular casts; many red and white cells.
12/7/50							4·5 {A=2·1 G=2·4		

* Amended from low-power figure.

with slight puffiness of the face and swelling of both legs extending to the knees. Examination revealed no abnormalities apart from oedema, albuminuria, and cylindruria. The injections were discontinued; she was placed on a low-fluid, low-salt diet, and advised to rest as much as possible. On October 5, she stated that she felt better; the puffiness of the face had diminished, but the ankles continued to swell if she walked. Rest in bed and a high-protein, low-salt diet were advised.

On December 8 she was admitted to the Cardiff Royal Infirmary with progressive oedema of the legs and ascites. Examination showed her general condition to be fairly good. The blood pressure was 160/100, with no cardiac abnormalities. Bilateral pleural effusions and ascites were present. The liver and spleen were not enlarged. Marked oedema was present in the feet, legs, thighs, abdominal wall, and lumbo-sacral area of the back. The Wassermann reaction was negative. By December 12 the oedema had spread to the front of the chest and to the face. Acupuncture of both legs was performed on two occasions, several hundred ounces of fluid being withdrawn. The patient now felt much more comfortable, although the oedema had generally increased, and she was discharged from hospital on January 31, 1950. While in hospital her urinary output had never exceeded 26 oz. daily. It was considered that she was suffering from a nephrotic lesion due to sodium bismuth tartrate therapy.

She now came under the supervision of the first hospital again. During May, 1950, she was admitted on three occasions for paracentesis abdominis and acupuncture of legs—about 300 oz. being withdrawn each time. She was last admitted on June 24. Examination then showed marked anaemia, gross oedema of the face, legs, and abdominal wall, and marked ascites. The blood pressure was 180/115. The heart was not enlarged. Numerous adventitial sounds were heard in all areas of the chest. Marked oedema of the whole body gradually developed. Paracentesis abdominis on July 11 and 16 produced about 12 pints of fluid each time. Pericarditis developed, her general condition deteriorated steadily, and she died on July 18, 1950.

Discussion

The pharmacological investigations of sodium bismuth tartrate and the bismuth compounds carried out by Longley, Clausen, and Tatum (1940) indicated the similarities rather than the differences between these compounds and suggested that bismuth compounds acted in a form common to all and not in the form of the compound injected. Subsequently Clausen, Longley, Green, and Tatum (1942) noted that bismuth preparations manifested their therapeutic activity as well as toxicity in direct proportion to their elemental bismuth content. Sollmann (1948) also pointed out that:

> the close correlation of toxic and therapeutic action on intramuscular injection indicates that the potency in both respects is determined by the concentration of bismuth and not by the nature of the original compound.

The concentration of bismuth will, of course, depend on the rate of absorption and excretion. Sollmann, Cole, and Henderson (1933) found that the percentage urinary excretion (the main route) was nearly uniform for all bismuth compounds—15 to 25 per cent. within 3 weeks. Sollmann (1948) later noted that about half of the retained bismuth was excreted in the first 3 weeks after administration was stopped, while the remainder was tenaciously retained.

The distribution of bismuth in the internal organs is of interest. According to Leonard (1928):

> All investigators employing a variety of bismuth drugs and of analytical methods arrive at a uniform result—the kidneys contain the highest percentage of bismuth.

Oettingen (1930) noted similar results in man following parenteral administration. Histological lesions in the kidneys have also been recorded. Brown, Lucia, and Mills (1938) described destruction of the convoluted tubules in rabbits following intravenous administration of sodium bismuth tartrate.

Nephritis occurs among the clinical systemic toxic manifestations of bismuth therapy listed by Goodman and Gilman (1941). They commented that the accumulation of the element at the site of excretion favoured renal damage:

> Nevertheless, as used clinically it rarely causes impairment of renal function or urinary evidence of parenchymatous damage.

Kolmer, Brown, and Rule (1939) pointed out that the kidney lesion was essentially nephrotic, and that the nephrotoxic effect was related not only to elemental bismuth, but to the rate of its dissociation, absorption, and excretion. Although deaths from renal toxic effects following therapy (for syphilis and other conditions) with various bismuth compounds have been described, no cases so far have appeared incriminating sodium bismuth tartrate in ordinary doses as the cause of fatal renal tubular lesions. Dowds (1936) reported three delayed deaths following subcutaneous sodium bismuth administration in gross over-doses (approximately 25, 13, and 25 gr.); two of these cases showed marked renal symptoms and autopsy revealed kidney damage.

The bismuth preparation used in the case here reported contained 1 gr. sodium bismuthyl tartrate B.P. in 1 ml. isotonic dextrose solution. Approximately 1 gr. of elemental bismuth was administered. Within 11 weeks of the initiation of therapy the patient developed oedema, heavy albuminuria, and

cylindruria. Subsequently the full typical nephrotic syndrome became manifest, and, despite temporary improvement, nitrogen retention developed and uraemic features preceded death. Although sodium bismuth tartrate is generally safe, it has been established, as indicated above, that all bismuth compounds may be cumulative and toxic, the toxicity depending on the bismuth content. Equally clear is the liability of sodium bismuth tartrate and other compounds to produce renal damage. Despite the small total intramuscular dosage the drug would appear to be responsible for the renal damage in this case.

Summary

(1) A case of nephrotic syndrome is described in a 39-year-old female following the injection of 2·5 gr. sodium bismuth tartrate for rheumatoid arthritis.

(2) It is noted that bismuth compounds, probably acting in a form common to all, manifest their therapeutic activity and toxicity in proportion to their elemental bismuth content.

(3) The danger of cumulative effect is indicated.

(4) Amongst the toxic effects, renal damage, which may be fatal, as in this case, is emphasized.

I am indebted to Dr. Leonard Howells for permission to publish this case, and for helpful advice and criticism.

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Syndrome néphrotique apres traitement d'arthrite rhumatismale par le tartrate sodique de bismuth

Résumé

(1) On décrit un cas de syndrome néphrotique chez une femme de 39 ans survenant après l'injection de 2,5 gr. de tartrate sodique de bismuth pour traiter d'arthrite rhumatismale.

(2) On note que les composés de bismuth, doués tous probablement d'une action similaire, manifestent leur activité thérapeutique et leur toxicité en fonction de leur teneur en bismuth pur.

(3) On indique le danger de l'effet cumulatif.

(4) On souligne, parmi les effets toxiques, la lésion rénale qui peut être mortelle, comme le montre le cas décrit.

Síndrome nefrótico después del tratamiento de la artritis reumatoide con el tartrato sódico de bismuto

Sumario

(1) Se describe un caso de síndrome nefrótico en una mujer de 39 años ocurriendo después de una inyección de 2,5 gr. de tartrato sódico de bismuto al tratar su artritis reumatoide.

(2) Se nota que los compuestos de bismuto, todos probablemente dotados de una acción similar, manifestan su actividad terapéutica y su toxicidad en función de su tenor de bismuto puro.

(3) Se indica el peligro del efecto cumulativo.

(4) Se hace resaltar, entre los efectos tóxicos, la lesión renal que puede ser mortal, como en el caso descrito aquí.

BOOK REVIEWS

Cortisone et Corticostimuline (ACTH) en Rhumatologie. By F. Coste, J. Cayla, and F. Delbarre. 1953. Pp. 414. Masson, Paris. (2,800 *Frs*; 63*s*.)

In the foreword the authors point out that, although Hench, Kendall, and their collaborators still refer to work with cortisone and ACTH as a "therapeutic experiment", this attitude is no longer tenable. These drugs are being used so widely in the field of rheumatic and other diseases that discussion on their value can no longer remain in the field of pure science.

The present work deals only with the rheumatic and para-rheumatic diseases, and is concerned with decisions as to its suitability in certain cases and the best methods of administration. The experience has been gained in the study of over 460 cases of rheumatic disease, mainly at the Hôpital Cochin in Paris, and the findings are compared with those of other workers, particularly with reports from America.

Early in the book the complications of hormone therapy are discussed, and it is pointed out that side-effects relating to the skin, locomotor system, and nerves are annoying and may be unattractive and at times even painful, but that they only rarely prove a real obstacle to the continuation of treatment. Endocrine and metabolic troubles such as steroid diabetes have been mild and tolerable. Major adverse incidents comprise vascular accidents, oedema, infections, digestive disturbances, and changes in the mental condition of the patients. Hypertension, usually mild, is occasionally progressive and may require administration to be stopped, but it is transitory and always disappears when the drugs are omitted.

The possibility of hypercholesterolaemia with a predisposition to athero-sclerosis as a consequence of prolonged treatment with cortisone is considered to be merely a hypothesis. Thrombo-embolic accidents are stated to be poorly evaluated in the various reports. It is believed that if their existence is confirmed a more complete study would lead to the risk being minimized. Oedema and sodium retention have been observed with both hormones. They are not considered to be serious complications and can easily be rectified by the exclusion of salt from the diet and the use of diuretics.

The possibilities of infections occurring during treatment are manifest, particularly during periods of high dosage. Staphylococcal, pneumococcal, and especially virus infections may be aggravated, even provoked. Present or recent tuberculosis is a usual contraindication to hormone therapy, and the lungs should be *x*-rayed at frequent intervals during extended courses of treatment. The risk of infection is lessened by the fact that the hormones do not interfere with the action of antibiotics. Gastric hypersecretion is caused by the hormones; it is necessary and easy to neutralize this and so avoid the ulceration which may complicate treatment.

The authors consider that mental risks comprise the greatest danger in this therapy. They recommend that a rigorous psychiatric examination should be carried out before treatment is started, so that any warning symptoms can be recognized at once.

It is pointed out that treatment with cortisone and ACTH is long, difficult, and full of disappointing phases, and that as much publicity has been given to the risks as to the successes, so that the patients themselves may be worried about possible complications. Continued surveillance is therefore imperative, and hormone treatment should be refused to the anxious or unstable patient. The financial aspect must also be borne in mind.

In discussing the choice of hormone, there is no doubt that cortisone is the more convenient, and possibly more exact, but that ACTH may be superior when a rapid response is required, or perhaps in the initial stage of treatment. It is recommended that the suprarenal response be checked by means of Thorn's test before treatment is started, but it is emphasized that clinical response is still the only real method of evaluation.

The importance of a gradual reduction of dosage as recommended by both Hench and Boland is confirmed, either when long-term maintenance therapy is contemplated, or when a course of treatment is being terminated. The length of remission in rheumatoid arthritis after an initial period of treatment is considered; in the authors' experience with 94 patients, it lasted more than 2 months in only 18 per cent. They incline to Hench's opinion that the 10 per cent. of cases going into remission is significant; in their experience there seems to be no correlation between the length of remission and the length of treatment, and neither the sex nor the age of the patient, nor the duration of the disease appear to be determining factors. The erythrocyte sedimentation rate gave no indication of the likelihood of a remission after treatment.

The authors have done some interesting work on the various combinations of the two hormones in rheumatoid arthritis. The figures are small, but the work has been carefully evaluated. ACTH before cortisone gave satisfactory results, as did simultaneous administration and alternate short and long courses of each drug. The results of giving cortisone and ACTH on alternate days were not impressive. The most encouraging method is to give ACTH at the end of a course of cortisone; there appears to be no danger in this, and with the possibility of stimulating the suprarenal there is more hope of preventing a relapse on withdrawal.

The phenomenon of relapse after the withdrawal of these hormones has also been studied. The authors point out the importance of objective assessment, as the patient, often forgetting his pretreatment condition, may exaggerate the activity of the disease. In their cases the

number of relapses was less after ACTH than after cortisone, but they were unable to find any correlation between either the length of disease or the sedimentation rate and the relapse rate.

The following cortisone "sparers" were tried and found ineffective: insulin, *para*-aminobenzoic acid, adrenaline, oestrogens, progesterone, testosterone, DOCA, and pregnenolone. The authors feel that any infection should be treated, but, in disagreement with American and English workers, are cautious about using physiotherapy as these patients are apt to do too much on their own, and the danger arises that joints may be worked too hard.

The combination of the hormones and chrysotherapy has been studied. The advantage of simultaneous administration is that under hormone protection a therapeutically active total dose can be introduced more rapidly, and they have given as much as 1·36 g. gold in 5 days with intravenous ACTH. There is, however, a danger that gold intolerance may appear in the post-hormonal phase, and this is more likely to be an urticarial than an eczematous or erythrodermial reaction. It is believed that gold becomes ineffective or harmful when given in the later stages of long-term cortisone treatment, and that it should be forbidden in the posthormonal period as it does not prevent a relapse, and there is a grave risk of serious intolerance to the metal.

These authors believe that benefit can be obtained from the combination of orthopaedic surgery, particularly arthroplasty, and the hormones, as these permit early resumption of mobility and shorten the painful period of rehabilitation. They point out that surgeons have not proved that there is any delay in healing, and stress the fact that cortisone or ACTH treatment should not be interrupted during the surgical phase of treatment.

The practicability of short or long-term treatment is discussed at length. Although only one-quarter of their own cases which received successive courses of treatment, showed any appreciable benefit, the authors believe that intermittent treatment offers the arthritic patient a good chance of improvement. They suggest a number of short courses of combined cortisone and ACTH separated by short intervals; a high initial sedimentation rate is no contraindication, but where it returns rapidly to its former level on stopping, continuous treatment should be considered. They agree with Hench that intermittent therapy is indicated, particularly where posthormonal relapses are incomplete and slow, or where patients, particularly at the menopause and in adolescence, are relatively intolerant to the hormones, or where high doses are necessary for suppression of the disease.

It is considered impossible at present to say whether long-term maintenance therapy is practicable. Some authorities report very favourable results and others less favourable. The role of these hormones in rheumatoid arthritis cannot yet be compared with that of insulin in diabetes, DOCA in Addison's disease, or thyroxine in myxoedema. It is not yet known whether the body will be able to stand indefinitely the effects of cortisone and ACTH on the haemopoietic, lymphoid, and nervous systems, or how the results of continuous hormone therapy compare with the suffering and gravity of severe polyarthritis. Neither optimism nor pessimism is justified, and conclusions will have to await the results of the further studies now being carried out in many centres.

From their experience with polyarthritis in children, these workers conclude that this form of the disease responds as well as the adult type; that the hormone dosage can be proportionately higher than for adults as the children's power of toleration seems better; that minor side-effects, except for moon-face and obesity, are no more troublesome than in adults; and that the more serious side-effects such as hypertension and mental symptoms are less to be feared.

The results in ankylosing spondylitis have not been so good, with less effect on the pain, more severe relapses on stopping treatment, and less response to succeeding courses, so that continuous maintenance therapy is preferred in this disease. The hormones have been of great use in conjunction with arthroplasty of the hip.

In France much attention has been paid to the effect of the hormones in non-inflammatory and non-articular rheumatic conditions. In osteo-arthritis of the hip, high dosage was given for short successive periods; out of 23 cases, thirteen were relatively successful, and in these there was a history of infection, severe anatomical damage, and an alteration in the sedimentation rate.

Lesions of the intervertebral disks have been treated with success in a good proportion of cases of sciatica, lumbago, and cervical root compression. It is considered that the inflammatory element in these cases is favourably affected.

In acute peri-arthritis of the shoulder, moderate doses often produced excellent results as long as the drug was continued for a minimum of 14 days. In the more chronic cases the response was good, though it did not appear until 12 or more days of cortisone therapy had been given. In the "frozen shoulder" group, the results were less good, and it is considered that long periods of treatment are necessary. Other series in France have shown better results.

The authors are impressed with their short experience of hydrocortisone for intra-articular injection, of which they report 149 cases, mainly into knee joints.

Professor Coste and his colleagues give an interesting appreciation of the present position of hormone therapy in the rheumatic diseases from their own experience. They believe the hormones to be valuable in the treatment of rheumatic fever, and prefer ACTH to cortisone because of its more rapid action. In gout they have no doubt of the remarkable effect, but consider that hormones should only be used where there is no response to colchicine, and that they must always be followed by this drug.

In the more chronic rheumatic conditions, the main difficulty is the possibility of complications, and they consider that there is a risk of serious psychosis in 1 per cent., and the same for digestive troubles. In long courses, 10 to 15 per cent. are liable to serious complications.

On the whole they prefer continuous to intermittent treatment, and have some patients who have been on such a regime for over 2 years. They believe there to be

a case for such treatment in every variety of the disease, save perhaps in early cases which may go into remission spontaneously. Severe progressive rheumatoid arthritis provides many difficulties, but good results may be achieved, and in the long-standing crippled cases a combination of hormone therapy and orthopaedic treatment should be considered. They have also been impressed with the action of these drugs in scleroderma.

They conclude by stating that cortico-suprarenal hormone therapy has become a part of current practice for rheumatic conditions, both acute and chronic. They believe this to be warranted by the good results obtained, as compared to the ineffectiveness of other treatments, but feel disquieted because of the risks which are run when these drugs are used, and the uncertainty, as yet, of the long-term results. They stress the need for further research, particularly on mixed courses of cortisone and ACTH, the combination of chryso- and hormone therapy, and the local use of hydrocortisone. OSWALD SAVAGE.

Les Rhumatismes en Médecine et dans la Société. By François Françon. 1952. Pp. 158. Editions Universelles, Paris.

This pocket edition was written with the intention of presenting rheumatism and its social aspects to the non-specialist and to the cultured public.

The difficulties of a comprehensive classification of the rheumatic diseases are fully discussed in the introduction. The author, however, comes to a compromise by closely following the nomenclature recommended by the Rheumatism Commission of the French Ministry of Health (Paris, 1937), which is in many ways similar to the British classification suggested by the Royal College of Physicians in England. A useful table is then drawn under sixteen headings of the differences existing between the inflammatory and degenerative forms of rheumatism. Rheumatic fever (maladie de Bouillaud) is fully described, and its classical treatment by salicylates is discussed at length. The uses of ACTH and cortisone, and the prophylactic application of sulphonamides and penicillin, are briefly reviewed.

The chapter on the chronic forms of rheumatism gives to the reader a very good clinical picture of the different grades of rheumatoid arthritis, and treatment is discussed under the headings of internal medication, hygiene, diet, physical methods and orthopaedic measures. Though ACTH and cortisone may have their uses, gold remains the only drug which has stood the test of time.

Ankylosing spondylitis is included with Still's disease, and psoriatic arthritis as a sub-variety of rheumatoid arthritis. The plan of treatment here is slightly too rigid. The use of a full plaster of paris jacket for several months would not be approved by many rheumatologists.

Tuberculous rheumatism, a French concept, is described as a clinical entity, a point of view which is hardly accepted in England and is rejected in America.

The available space has not permitted a description of the degenerative types of arthritis, but for those who can read French, this excellent little book will be found to be a helpful reference for diagnosis and treatment.

M. H. L. DESMARAIS.

Report on an Enquiry into the Aetiological Factors associated with Rheumatoid Arthritis. Prepared by E. Lewis-Faning. *Annals of the Rheumatic Diseases*, Suppl. Vol. 9, 1950. British Medical Association, London. (7*s.* 6*d.*)

The Empire Rheumatism Council's statistical investigation into thirteen possible aetiological factors and thirteen clinical features of rheumatoid arthritis was published in a special supplement to the *Annals of the Rheumatic Diseases* in 1950. The investigation entailed the detailed study of 532 cases and 532 controls and the analysis of the results. It was a time-consuming and expensive venture, unique in this field, and produced many interesting facts, invaluable to further workers, though perhaps disappointing in the lack of dramatic findings. The conclusions of this report occasioned a spate of critical correspondence, disagreeing with the negative findings on certain aetiological factors. Such unexpected negative findings are very valuable, as they cause people to think again, though they do not prove that these factors have no effect whatsoever on the rheumatoid state.

The sex incidence was 100 males to 162 females, and it was found that the risk of developing the disease rose between the ages of 20 and 50 years. One of the surprising features was the absence of significant increase in psychological trauma in the patients as compared with the controls. There was no tendency to association with allergic disease, but focal sepsis was slightly more common in the rheumatoid group. A familial tendency was statistically proved. 24 per cent. of cases had commenced at the menopause. In considering working and home conditions, cold appeared as the only factor which tended to increase the risk of rheumatoid arthritis. Peripheral vascular instability occurred in nearly five times as many rheumatoids as controls, and frequently antedated the onset of the arthritis.

Undue fatigue, loss of weight, transient pains, and sweating were frequent prodromal symptoms. The onset was febrile in 14 per cent. and acute in 44 per cent.; 81 per cent. consulted their doctor within 3 months of the onset of symptoms. 12 per cent. of the rheumatoid cases had nodules. Only 7 per cent. had normal sedimentation rates.

These are some of the findings discussed in the Report, which should be studied in full. G. D. KERSLEY.

Rheumatic Fever. A symposium edited by Lewis Thomas. 1953. Pp. 349, 56 figs, 59 tables. University Press, Minnesota. Geoffrey Cumberlege, London. (80*s.*)

This is the report of the 29 papers and the consequent discussions which were contributed to a symposium held at the University of Minnesota in November, 1951. The publication of such symposia is an increasingly common practice which often lacks adequate justification. Sometimes the delay in publication is so great that the rapid advance of research has raced ahead of the contributors; sometimes the real merit of such symposia lies in the free exchange of ideas between writers in separate but contiguous fields and the printed page fails to recapture the

value of such stimulating exchanges. This volume can, however, be unreservedly recommended. Many of the contributors, such as McQuarrie, Duckett Jones, G. E. Murphy, Ann Kuttner, M. J. Shapiro, and F. F. Schwentker, have already made substantial advances in our knowledge of rheumatic fever, and other writers whose names are unknown to the reviewer here make impressive contributions.

It is more than twenty years now since Alison Glover wrote of rheumatic fever as an obsolescent disease, and it is to his credit that time has proved his hopeful forecast false. For rheumatic fever is still an implacable and unconquered enemy of mankind. During the last six months there has been a marked recrudescence of acute rheumatism in children in areas where the disease has been quiescent for two or three years ; and it should be continuously remembered that as many hearts are being quietly crippled by one insidious attack as are damaged by overt rheumatism. These papers not only deal with the natural history, prophylaxis, and treatment of acute rheumatism; their especial value lies in their recognition that it is only by the elucidation of the peculiarities of the individual host that full understanding will be achieved.

Murphy gives a masterly review of the histopathology of rheumatic fever and advances the view that the Aschoff bodies are formed from the damaged myocardial fibres. There is a useful paper by H. L. Hodes on non-rheumatic myocarditis, which emphasizes the non-progressive nature of this cardiac damage compared with that of rheumatic fever. Several papers discuss the acute-phase reactions, including the measurement of hyaluronidase inhibitor, C-reactive proteins, and antibody responses, and demonstrate that, while such tests are of increasing value, they are not yet of specific diagnostic quality. Dorfman contributes an enlightening paper on the biochemistry of connective tissue and rheumatic fever. It was news to the reviewer that the only mammalian organ which has been proved to contain hyaluronidase is the testis. Well-balanced surveys by Rammelkamp on the prevention of rheumatic fever and by Shapiro on its management conclude an admirable volume.

DOUGLAS HUBBLE.

NEW YORK RHEUMATISM ASSOCIATION

ANNUAL MEETING, 1953

The Annual Meeting of the New York Rheumatism Association was held at the Cornell University Medical College, New York, on April 8, 1953. Dr. Charles Ragan presided, and the following papers were given:

Relationship of Sensitized Sheep Cell Reaction to Rheumatoid Arthritis. By Ronald W. Lamont-Havers (*Presbyterian Hospital*).

Long-Term Therapy of Rheumatoid Arthritis with PABA and Cortisone. By Leon L. Wiesel and A. Sidney Barrit (*Brooklyn Hospital*).

Altered Hepatic Function in Rheumatoid Arthritis; Effect of Butazolidin Therapy. By Jack R. Dordick and Hyman Bakst (*Beth Israel Hospital*).

Chordotomy in the Treatment of Osteo-Arthritis of the Hip. By Byron Stookey (*Neurological Institute*).

Absorptive Arthropathy. By Murray Silver and Otto Steinbrocker (*Hospital for Joint Diseases*).

Dissemination of Chronic Discoid Lupus Erythematosus. By Jerome Simson (*Third (New York University) Division, Bellevue Hospital*).

The following officers and executive committee members were elected for 1953-54:

President:	Robert M. Lintz
Vice-President:	Jed H. Irvine
Secretary-Treasurer:	Bernard Rogoff
Executive Committee:	Charles Ragan
	William Kammerer
	Robert L. Preston
	Edward F. Hartung
	Currier McEwen
	Charles M. Plotz

CORRIGENDUM

Annals of the Rheumatic Diseases (1953), **12**, 49. In the list of Officers of the Heberden Society for 1953, the initials of Dr. Ernest Fletcher should appear as E.T.D. (not E.G.E.).

EMPIRE RHEUMATISM COUNCIL

SIXTEENTH ANNUAL REPORT

The sixteenth annual report of the Empire Rheumatism Council was presented by the Chairman, Lord Horder, at the Annual General Meeting held on April 29, 1953, at 11 Chandos Street, London, W.1. The Chairman first recorded with regret the deaths of Lord Broadbridge, Vice-President of the Council, and Mr. H. L. Jackson, Life-Councillor.

The incorporation of the Council had brought about an enlarged membership, and he hoped that their new friends would be active in spreading interest in their work.

Research.—The work of the Council in this field had been greatly increased in the past year. Dr. A. A. Henly assisted by Miss M. I. Potter had continued his work at the Hospital of St. John and St. Elizabeth on ACTH and cortisone, particularly on their relation to urinary steroid excretion. "Butazolidin" was found to have little or no effect in this direction, though clinically useful in other respects. Their thanks were due to Messrs Roche Products Ltd. for financing this work.

The work of Dr. J. D. Billimoria at the Westminster Hospital Medical School had been greatly assisted by the fact that the School had provided a high pressure autoclave for carrying out dehydrogenation reactions.

The holders of the "Elizabeth Macadam Fellowship" had sent in excellent reports of progress. Dr. J. L. Potter had completed his studies on ankylosing spondylitis chiefly in relation to radiotherapy at the Northern General Hospital, Edinburgh, under Dr. J. J. R. Duthie; Dr. B. F. Matthews had been investigating physical and biochemical changes in ageing human cartilage at the Canadian Red Cross War Memorial Hospital, Taplow, under Dr. E. G. L. Bywaters.

Dr. J. M. Tweed, the first "Philip Gray Fellow", had been working on the causation of rheumatoid arthritis at the West London Hospital under Dr. W. S. C. Copeman.

An application had been received from Dr. E. Wittkower of McGill University, Montreal, who was undertaking a study of "Rheumatoid Arthritis in Two Contrasting Communities", and the Treasury had been asked for permission to transfer sterling currency to Canada.

An offer from the Merck Co. of the U.S.A. to supply sufficient cortisone acetate to maintain fifty patients on oral therapy for 12 months (and also to maintain *in perpetuo* those patients who remained on therapy after that time) had been gladly accepted by the Executive Committee. It was proposed to carry out trials of cortisone and aspirin at nine British centres in 1953.

It had been decided by the Scientific Co-ordinating Committee that two Empire Rheumatism Council fellowships should be awarded in 1953 for the study of:

(*i*) the adrenal hormones

(*ii*) the proteins in connective tissue.

Special biopsy needles had been designed and made for use at the West London Hospital through the generosity of Mr. D. D. Mynott.

Education.—All the Regional Hospital Board areas were now represented on the Regional Sub-Committee and this committee had begun by obtaining information on the state of facilities for rheumatism treatment and research in each area. The Post-Graduate Lecture Demonstrations had been continued at the Arthur Stanley Institute, Middlesex Hospital, and instructive clinical meetings held by the Heberden Society had been well attended.

Members had been invited to the International Congress of Physical Medicine in 1952, and a good many members proposed to attend the Congress of the European League against Rheumatism at Geneva and Aix-les-Bains in August, 1953.

Commonwealth.—The branches in Canada, Australia, New Zealand, affiliated to the Council continued to report satisfactory progress and it was hoped that as soon as a representative appointment for Canada was made, a further Commonwealth Sub-Committee Meeting would be arranged. Copies of the minutes of meetings received from the Dominions disclosed that all three autonomous affiliated branches were forging ahead. Dr. A. J. Cronin, President of the New Zealand affiliated branch, had had the opportunity of joining their deliberations by attending various meetings and conferences whilst in England.

Finally, the Chairman commended the loyal and devoted services of the members of the key administrative committees, whom it was proposed to re-elect for a further term of office, and he congratulated the Finance Committee upon the skilful management which had enabled it to show a surplus at the end of the year.

NEW OFFICERS

At the Annual General Meeting, Lord Horder, who has been Chairman of the Council since 1936, announced his resignation. Dr. W. S. C. Copeman was elected in his place, on the proposition of Lord Webb-Johnson, who was re-elected Vice-Chairman. Dr. Oswald Savage was elected Honorary Medical Secretary, and Dr. R. M. Mason deputy Medical Secretary.

CORONATION LECTURE

Professor Sir Henry Cohen will deliver a lecture on "The Concept of Collagen Disease" at the Royal Society of Medicine (Barnes Hall), 1 Wimpole Street, London, W.1, on Thursday, July 2, 1953, at 8.15 p.m.

LIGUE INTERNATIONALE CONTRE LE RHUMATISME

EIGHTH INTERNATIONAL CONGRESS, 1953

(THIRD ANNOUNCEMENT)

The principal speakers on the four main topics for discussion at the International Congress to be held in Geneva from August 24-28, 1953, will be as follows:

(1) **Connective Tissue** (J. H. Kellgren, *Manchester*, G. Teilum, *Copenhagen*, E. Hartmann, *Göttingen*, and C. Ragan, *New York*).

(2) **Steroid Hormones** (T. Reichstein, *Basle* (Nobel Prizeman, 1950), P. S. Hench, *Rochester, U.S.A.* (Nobel Prizeman, 1950), F. Coste, *Paris*, and A. Ruiz Moreno, *Buenos Aires*).

(3) **Surgery in the Treatment of Rheumatism** (R. Judet and R. Merle d'Aubigné, *Paris*, J. Permanyer Vilardell, *Barcelona*, and Dr. Brown, *Cleveland, U.S.A.*).

(4) **Rehabilitation of the Disabled** (W. Tegner, *London*, H. Rusk, *New York*, G. Edström, *Lund*, and Dr. Hoske, *Cologne*).

Further information may be had from the Chairman of the Organizing Committee, Prof. K.-M. Walthard, Institut de Physiatrie, Hôpital Cantonal, Genève (Telegrams: Rhumatisme Genève). Travel and accommodation will be arranged by the American Express Company, to whom all applications should be made. (See also the March issue of this Journal, p. 47.)

Those desiring to attend the congress are asked to register as soon as possible in order to be certain of accommodation.

CANADIAN ARTHRITIS AND RHEUMATISM SOCIETY

The Saskatchewan radio stations broadcast four talks during March, 1953, to encourage the public to seek medical advice for joint pain and swelling at an early stage to lessen the risk of serious disablement. Drs D. E. Roger, Wendell Macleod, T. E. Hunt, S. C. Heal, and C. L. Comrie, together with physiotherapists, technicians, and patients, co-operated in the broadcasts.

In Manitoba members of the St. John Ambulance Brigade are helping to make simple appliances and equipment to assist patients in their own homes. A new physiotherapy centre has been opened in Winnipeg. In Toronto, Ontario, arrangements have been made for swimming classes for arthritis patients at the Sunnybrook Veterans Hospital. In Ottawa special attention is being given by occupational therapists to assisting the arthritic housewife in her duties.

The Society is finding that the Mobile Arthritis Unit, combined with these various forms of assistance and service to patients in their own homes, is bringing valuable aid to many sufferers at a fraction of the expense entailed by full-time hospital treatment.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section " ACTH, Cortisone, and other Steroids " includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Rheumatic Disease of the Coronary Arteries in Childhood. (Ревматические коронариты в детском воэрасте.) YAKUB, E. E. (1952). *Pediatriya*, **32**.

A statement of Skvortsov (1950) is quoted to the effect that the commonest cause of death in acute rheumatism in children is myocarditis and pericarditis, and next to these, coronary vascular disease. In the present series of twelve cases in which the clinical picture of coronary disease was present, eleven of the patients were between 11 and 14 years old and one was aged 8; four were males and eight females; three were in the acute phase of their first attack, while nine were suffering from an acute recrudescence. Sudden onset of pain in the neck or shoulders, dyspnoea, cyanosis or pallor of the face, and a subjective feeling of terror and tachycardia (or, rarely, of bradycardia) were the presenting symptoms. The electrocardiogram showed the typical signs of coronary involvement.

Treatment included the administration of 1 or 2 drops of 1 per cent. trinitrin in spirit, morphine, and oxygen inhalations. The immediate prognosis was good, but the ultimate outlook poor. In fatal cases brought to necropsy no infarcts were usually found, but the smaller branches of the coronary arteries showed fibrinoid necrosis and thickening of the vessel walls. The larger vessels were less frequently involved. The author pleads for a more thorough investigation of the subject.

L. Firman-Edwards.

Prevention of Cardiac Lesions in Acute Articular Rheumatism. A New Method in the Treatment of Rheumatic Fever. [In English.] CORELLI, F. (1952). *Acta med. scand.*, **143**, 450. 1 fig., 10 refs.

A new treatment for rheumatic fever, founded on the hypothesis that the disease is of allergic-hyperergic pathogenesis, consists in:

(1) administration of amidopyrine, anti-histaminics, and calcium;

(2) avoidance of stimulating treatment;

(3) absolute rest in bed until the erythrocyte sedimentation rate is normal;

(4) administration of oxygen by nasal tube or mask for 2 or 3 weeks or longer.

It is claimed that there was no evidence of a cardiac lesion after $2\frac{1}{2}$ years in any one of a series of fifty successive cases of a first attack of rheumatic fever, treated in this way, at any early stage, before the onset of cardiac signs.

[Reference to the case reports suggests that not every patient was followed-up for $2\frac{1}{2}$ years after the initial attack. The most interesting clinical feature of this communication is the statement that no case of agranulocytosis was observed amongst several hundred patients treated with amidopyrine. The evaluation of any new treatment for rheumatic fever is difficult owing to the variability of the cardiac findings and the latent period before they become clinically discernible. The author appreciates the latter but not the former, and it is to be regretted that a control series was not arranged.]

R. E. Tunbridge.

Treatment of Rheumatic Fever with ACTH. I. Smaller Doses of ACTH in Acute Rheumatic Fever. SHEINKOPF, J. A., GRIFFITH, G. C., MORRISON, R., and STARR, P. (1952). *Amer. J. med. Sci.*, **224**, 390. 2 figs, 14 refs.

At the Los Angeles County Hospital, California, the authors have observed the effect of small doses of ACTH. To twelve unequivocal cases of rheumatic fever ACTH was given intramuscularly in divided doses at the rate of 0·4 mg./kg. body weight, the total dose ranging between 20 and 24 mg. per day. The cases were selected as being neither severe nor complicated; the mean duration of treatment was 20·5 days. This dose was found to be effective in mild cases and the patients' signs and symptoms disappeared. In the moderately severe cases such a dose was not effective. Whilst ACTH appears to lessen the inflammatory reactions of the disease, there is no proof as yet that it is effective in preventing disabling heart disease.

D. P. Nicholson.

II. ACTH by the Continuous Intravenous Drip Method. GRIFFITH, G. C., SHEINKOPF, J. A., MCNAIR J., D., and STARR, P. (1952). *Amer. J. med. Sci.*, **224**, 397. 3 figs, 13 refs.

At the Los Angeles County Hospital, ACTH was given to 37 consecutive cases of rheumatic fever without regard to their severity, chronicity, or the presence of

heart failure. Three methods of treatment were used:

(1) ACTH in divided intramuscular doses amounting to 100 mg. per day;

(2) small doses by continuous intravenous drip;

(3) the consecutive use of both these methods.

The need for higher dosage became apparent when the more protracted cases failed to respond to small doses.

The response to this type of treatment was dramatic, and the only case which failed to respond was shown to be suffering from subacute bacterial endocarditis. The chronic cases relapsed after cessation of treatment. It is concluded that the use of ACTH by intravenous drip results in a quicker response as judged by the resultant eosinopenia, and has the added advantage of being less costly as the amount of the drug was approximately one-tenth of that required by the intramuscular route. *D. P. Nicholson.*

Treatment of Acute Rheumatism with Heparin. (De behandeling van acute polyarthritis met heparine.) MENDES DE LEON, C. (1952). *Ned. Tijdschr. Geneesk.*, **96**, 2417. 3 figs, 27 refs.

The allergic nature of acute rheumatism is discussed in relation to the collagen diseases, and the various substances which have been used to suppress allergic phenomena are considered. The predominance of depolymerization of hyaluronic acid in the intercellular substance in hyperergic conditions is the indication for the administration of anti-hyaluronidase. Heparin, which is closely related chemically to hyaluronic acid, possesses anti-hyaluronidase activity, and the reported results of its use in acute rheumatism are quoted. The author reports favourable results in a few cases resistant to salicylates. *R. Crawford.*

Control of Rheumatic Fever Recurrences with Sulfadiazine and Gantrisin. BUNDY, W. E., MCCUE, C. M., and PORTER, R. R. (1952). *J. Pediat.*, **41**, 320. 3 figs, 17 refs.

In this paper from Richmond, Virginia, the authors report the results in 190 rheumatic children of giving continuous sulphonamide prophylaxis for periods ranging from 4 days [*sic*] to 76 months. All patients were followed up for periods ranging from 9 months to 11 years. There were four recurrences (2·96 per cent.) in 135 cases receiving sulphadiazine compared with three (4·6 per cent.) in the 64 cases taking "gantrisin" (sulphafurazole). Leucopenia (under 4,000 leucocytes per c.mm.) developed in nine (6·6 per cent.) of those on sulphadiazine and in four (6·2 per cent.) of those on gantrisin. *R. S. Illingworth.*

Treatment of Chorea in Children with Prolonged and Interrupted Sleep. (Leczenie plasawicy u dzieci przedluzonym przerywanym senm.) ROZA, N. (1952). *Pediat. polsk.*, **27**, 949. 3 refs.

The treatment of chorea with prolonged narcosis, which was introduced by Himelfarb of Smolensk in 1949, was used by the author in 25 cases at the Paediatric Clinic in Warsaw. The patients, twelve of whom were boys and thirteen girls, ranged in age from 5 to 14 years. In twelve cases there were signs of cardiac involvement, and in two cases the patient suffered also from tuberculosis. Only in two cases was the primary attack treated—one patient was in the fourth relapse and all others in the second relapse.

The treatment was based on the administration of phenobarbitone, 0·1 g. being given four times daily during the first 2 days, the dose gradually decreasing thereafter, treatment lasting 7 to 10 days in all. The patients were given a high-calorie diet supplemented by vitamins, being awakened only at meal-times. The results were very satisfactory, the choreic movements subsiding and the erythrocyte sedimentation rate falling in all cases, and electrocardiographic and radiological findings returning to normal in those with cardiac involvement. *J. Mester.*

Hemodynamic Studies in Rheumatic Heart Disease. FERRER, M. I., HARVEY, R. M., CATHCART, R. T., COURNAND, A., and RICHARDS, D. W. (1952). *Circulation*, **6**, 688. 9 figs, 15 refs.

At Columbia University and Bellevue Hospital, New York, the cardiac function in 42 patients with rheumatic heart disease was investigated by cardiac catheterization. Studies were made with the subjects at rest, in some cases after the administration of digoxin, and in others after exercise for at least 5 minutes.

In some patients with a diagnosable valve lesion but without symptoms the cardiac function was found to be normal. The occurrence of symptoms was always associated with an increase in pulmonary arterial pressure, though the level to which this was elevated was variable. An increase in pulmonary arterial pressure was not diagnostic of a lesion of any particular valve. In some cases of mitral stenosis it was considered that the pulmonary hypertension was due not only to the mechanical effect of the stenosis, but also to left ventricular failure. This conclusion was based on the effects of injected digoxin.

Exercise in the earliest stage of cardiac failure was associated with a normal increase in cardiac output, but at the expense of an elevated right-ventricular end-diastolic pressure. When congestive failure was present there were found consistently, even at rest and irrespective of any valvular lesions, a low cardiac output, pulmonary hypertension, an increase in blood volume, and elevation of the right-ventricular end-diastolic pressure. *H. E. Holling.*

Treatment and Prophylaxis of Juvenile Rheumatism. (Tratamiento y profilaxis del reumatismo infantil.) SELFA, F. (1952). *Med. esp.*, **28**, 463. 13 refs.

Results of ACTH Treatment of Rheumatic Fever in Children. (Wyniki leczenia acth choroby reumatycznej u dzieci.) MARCZUNDKA-ROBOWSKA, M. (1952). *Pediat. polsk.*, **27**, 1283. 10 refs.

Rheumatism in Childhood. (Rheumatismus im Kindesalter.) CATEL, W. (1952). *Z. Rheumaforsch.*, **11**, 331. 40 refs.

Cortisone in Rheumatic Fever. [In English.] BUNIM, J. J. (1952). *Stetoscopio*, **2**, 101. 2 figs, 10 refs.

Effects of Cortisone on Acute Rheumatic Carditis. GIBSON, H. C., SPIVEY, D. V., CLIFFORD, T. C., and OPPENHEIM, D. J. (1953). *U.S. armed Forces med. J.*, **4**, 295. 4 figs, 12 refs.

ACTH and Cortisone in Rheumatic Carditis. (De toepassing van ACTH en cortison bij carditis rheumatica.) CREVELD, S. VAN, and KUIPERS, F. (1953). *Maandschr. Kindergeneesk.*, **21**, 41. 3 figs, 34 refs.

Prevention of Rheumatic Heart Disease. STAFFORD, G. E. (1953). *Neb. St. med. J.*, **38**, 39. 6 refs.

Duration of Electrical Systole in Rheumatic Carditis. (Durata della sistole elettrica nella malattia reumatica.) BOCCARDELLI, V. (1952). *Progr. med., Napoli*, **8**, 662. 3 figs, 25 refs.

Observations on Treatment of Rheumatic Fever with Salicylate, ACTH, and Cortisone. I. Appraisal of Signs of Systemic and Local Inflammatory Reaction during Treatment, the Rebound Period and Chronic Activity. FISCHEL, E. E., FRANK, C. W., and RAGAN, C. (1952). *Medicine, Baltimore*, **31**, 331. 9 figs, 59 refs.

Antibiotics or Antipyretics in Rheumatic Fever? (Antibiotische oder antipyretische Therapie des Rheumatischen Fiebers?) HARING, W. (1952). *Ther. d. Gegenw.*, **2**, 406. 12 refs.

Present Status of Diagnostic Tests for Rheumatic Fever. MCCARTY, M. (1952). *Ann. intern. Med.*, **37**, 1027. 3 figs, 8 refs.

Recent Developments in the Prevention of Rheumatic Fever. HOUSER, H. B., and ECKHARDT, G. C. (1952). *Ann. intern. Med.*, **37**, 1035. 24 refs.

Prophylaxis of Rheumatic Fever. LEVY, D. F. (1952). *Conn. med. J.*, **16**, 899. 4 refs.

Natural History of Rheumatic Fever: A 20-Year Perspective. BLAND, E. F., and JONES, T. D. (1952). *Ann. intern. Med.*, **37**, 1006. 4 figs, 28 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Use of Massive-dose Cortisone in the Treatment of Rheumatoid Arthritis. CHASE, J. D., and LIGHTBODY, J. J. (1952). *J. Mich. med. Soc.*, **51**, 1167. 5 figs, 12 refs.

The authors, working at the Wayne University College of Medicine, Detroit, have treated four men and three women suffering from rheumatoid arthritis with doses of cortisone larger than those usually given. The drug was administered parenterally in several doses totalling 500 mg. or more daily in every case. This treatment was continued until toxic symptoms appeared, when administration was stopped abruptly in six cases and the dose gradually reduced in the seventh. The total dose of cortisone administered before the appearance of toxic symptoms ranged from 6·125 to 26·625 g. In all the patients there was marked improvement in the arthritic symptoms.

The toxic manifestations included frank psychosis, marked depression, hyperglycaemia, facial fullness, hypertension, duodenal ulcer, and paroxysmal tachycardia. In no instance did they persist longer than 3 months. The improvement in the arthritic condition was partly maintained in one patient for 230 days and in another for 78 days, but the other five patients relapsed in a few weeks.

Synovial tissue from the knee-joint, which was examined in four patients before and after treatment, showed no significant change in histopathology in two, and a reduction in the inflammatory reaction, but no alteration in the density of fibrous tissue, in the other two. A rise in the excretion of 17-ketosteroids and of gonadotrophins was demonstrated in the five cases in which the excretion was estimated. Examination of testicular biopsy specimens from four male patients after treatment failed to reveal any marked change compared with specimens examined before treatment.

The authors conclude that in rheumatoid arthritis short-term administration of large doses of cortisone has no advantage over long-term administration of small doses. *C. E. Quin.*

Observations on the use of Cortisone and Corticotropin in Rheumatoid Arthritis. PRICE, A. E., REVENO, W. S., LIGHTBODY, J. J., HEIDE, E. C. V., KASHTAN, H. A., and CORRINAN, K. E. (1952). *J. Mich. med. Soc.*, **51**, 1183. 7 refs.

The authors report the results of treatment of rheumatoid arthritis with cortisone (65 patients), ACTH (twelve patients), and intra-articular injections of hydrocortisone (three patients). Of the 65 patients receiving cortisone, 45 were treated for 2 years, the remaining twenty patients and those receiving ACTH or hydrocortisone being treated for a year or less. Cortisone was administered orally in maintenance doses of 25 to 75 mg. daily, and ACTH subcutaneously in maintenance doses of 10 to 25 mg. daily, except for a few patients who received 25 mg. thrice weekly. All the patients receiving cortisone and ACTH were given a diet of which the salt content was less than 1 g.

The results obtained with cortisone and with ACTH were similar; they were considered to be good in 74 per cent. of the patients receiving cortisone, and 77 per cent. of those receiving ACTH, and fair in 22 per cent. of the former group, and 15 per cent. of the latter. The complications were as follows: oedema (29 patients), facial hirsuties (27, mild in 21), thinning of the scalp hair (two), acne (fifteen), marked pigmentation (one), purpuric lesions (three), gastro-intestinal haemorrhage (one), gastric ulcer (two, with a perforation in one), euphoria (34), mild depression (six), acute depressive psychosis (one), schizophrenia (one), and hypertension (one). The 29 patients with oedema and the three with purpuric lesions

received cortisone, while the patient with pigmentation received ACTH.

A total of 94 injections of hydrocortisone were given to thirteen patients, in eight of whom the response was excellent, a decrease in joint swelling and an improvement in mobility lasting from 2 to 12 weeks being noted. Moderate benefit lasting a few days to 2 weeks was observed in three patients, while the remaining two did not respond satisfactorily.

The authors also measured the uptake of radioactive iodine by the thyroid in patients receiving cortisone or ACTH. It was found that cortisone depressed thyroid function and ACTH stimulated it. They point out, however, that their supplies of ACTH contained a trace of thyrotrophic hormone, which might explain the thyroid stimulation. *C. E. Quin.*

Review of Eighteen Months' Experience of the Treatment of Chronic Rheumatism with Cortisone and Corticotrophin. (Bilan de 18 mois de traitement du rhumatisme chronique à la cortisone et a l'A.C.T.H.) BLOCH, S. (1952). *Strasbourg méd.*, **3**, 727. 8 refs.

The results of treating 32 cases of chronic rheumatism with corticotrophin (ACTH) and cortisone are described. The series included 27 cases of chronic arthritis, two cases of ankylosing spondylitis, and one case of osteo-arthritis of the hips. Most patients were given ACTH first, in daily doses of 100 mg. to a total of 0·25 to 2·0 g. Those who failed to respond to ACTH were then given cortisone, 50 to 300 mg. daily, to a total of 0·5 to 4·3 g.

In 24 of the cases of chronic polyarthritis, definite improvement was obtained, minimal improvement occurring in the other three cases, one of which was of post-gonococcal arthritis. Relapse, however, took place in 10 to 14 days after cessation of treatment, with the exception of three cases in which improvement continued for 1 to 10 months. Of the two cases of ankylosing spondylitis, one was unaffected by cortisone, and the other, in which there was also aortic incompetence, developed subacute bacterial endocarditis during cortisone therapy (although the spondylitic symptoms were improved). The case of osteo-arthritis of the hips was unaffected by ACTH. It is concluded that ACTH and cortisone are useful in the treatment even of advanced cases of chronic polyarthritis, but that this treatment needs to be continuous. The hormones are particularly useful in improving and maintaining mobility in cases requiring orthopaedic operation. *Kathleen M. Lawther.*

Some Effects of Long-Continued Cortisone Therapy in Rheumatoid Arthritis. WEST, H. F., and NEWNS, G. R. (1952). *Lancet*, **2**, 515. 5 refs.

The authors, working at the Sheffield Centre for Rheumatic Diseases, report the results of administration of cortisone for periods up to 21 months to six patients with rheumatoid arthritis. The first three patients, females aged 16, 22, and 36 years respectively, received 50 to 75 mg. daily and responded well, though in one of them more joints were affected at the end of treatment than at the beginning. In all three menstrual function and feminine attributes became normal and remained so. In the fourth patient, a female aged 49, who was 3 years past the menopause, there was dramatic improvement at first with a dose of 50 mg. cortisone daily, but by the ninth month 150 mg. daily was barely sufficient to control the arthritic symptoms. On this higher dose abnormal deposits of fat and hypertension were observed, but these effects were reversed when the dose of cortisone was reduced to 75 mg. daily. Other complications included haemorrhage from a duodenal ulcer and severe hot flushes (relieved by oestrogen therapy). This patient's arthritic symptoms were worse after treatment than they had been before. The fifth patient, a man aged 29, received cortisone for one year; he then became ill with fever, tachycardia, and low blood pressure, and died on the fourth day of the acute illness. Necropsy revealed amyloid disease, the liver, adrenal glands, and spleen being involved. The sixth patient, a man aged 48, also received cortisone for one year. Haemorrhage occurred from a duodenal ulcer, but this condition responded to routine treatment. Cortisone therapy was stopped 25 days after the haemorrhage, and on the 30th day he collapsed and died. Necropsy revealed severe myocardial fibrosis and a healed duodenal ulcer. The adrenal cortex was histologically normal. *C. E. Quin.*

Abnormal Glycine Metabolism in Rheumatoid Arthritis. LEMON, H. M., CHASEN, W. H., and LOONEY, J. M. (1952). *J. clin. Invest.*, **31**, 993. 2 figs, 43 refs.

Writing from the Veterans Administration Arthritis Clinic, Boston, the authors point out that alterations in the polypeptide chains, the elements responsible for the tensile strength and elasticity of connective tissue, have not been adequately studied in diseases affecting this tissue. They also point out that the connective-tissue proteins, collagen and elastin, are unique in their composition in that glycine constitutes 22·8 to 27·6 per cent. by weight of these substances, and that they are thus quite unlike any other human extracellular or intracellular protein whose composition has been described. Any great increase in collagen synthesis in the body might therefore be reflected in an increased requirement for glycine which, though not an essential amino-acid, is limited in its rate of synthesis. Furthermore, it has been shown that a marked reduction in the rate of hippurate formation occurs in some cases of acute or advanced rheumatoid arthritis, and the authors were interested to determine whether this was due to the lack of synthesis of hippuric acid owing to poor liver function, or to lack of glycine. They therefore estimated the concentration of serum glycine during the rapid hepatic formation and renal excretion of glycine-benzoic acid conjugates (hippuric acid). At the same time the level of serum alanine was also determined, since this amino-acid is rapidly synthesized by the body and does not take part in the detoxication of benzoic acid.

The test was performed on 54 patients with rheumatoid arthritis and on 41 control patients. In 36 of the 41 control patients the serum glycine level had not changed by more than 15 per cent. at the end of one hour after the intravenous injection of 1·77 g. sodium benzoate, while in 35 of the 54 patients with rheumatoid arthritis the

serum glycine level had fallen by more than 15 per cent. Furthermore, in a few of the patients there was a direct correlation between the erythrocyte sedimentation rate and the fall in serum glycine level after sodium benzoate when these tests were repeated at frequent intervals. The excretion of hippuric acid was slightly greater in the patients than in the controls. There was no change in serum alanine levels throughout the investigation. The authors conclude that these findings suggest an abnormality of connective-tissue metabolism. *G. A. Smart.*

A Clinical Investigation of the Value of Synthetic Hyaluronidase Inhibitors in Rheumatoid Arthritis. (Klinisk prövning av syntetiska hyaluronidasinhibitorer vid reumatoid artrit.) HAHN, L., THUNE, S., and TRUEDSSON, E. 1952). *Nord. Med.*, **48**, 1615. 3 figs, 8 refs.

At the Rheumatological Clinic, Lund, Sweden, three synthetic hyaluronidase inhibitors (carboxyphenylmethanes) were given by mouth to 85 in-patients and sixteen out-patients with long-standing rheumatoid arthritis (mean duration 8 years) in whom the disease had recently been active for an average period of 12 months. There was pronounced subjective and objective improvement in the majority of cases within about 9 days of the start of treatment. There were no noteworthy side-effects although many patients complained in the first few days at being deprived of their salicylates.

[It is impossible to quote the actual percentage of patients improved because the authors report the effect of each compound separately on each of four symptoms and three physical signs.] *B. Nordin.*

Psoriatic Arthritis: Observations on the Clinical, Roentgenographic, and Pathological Changes. SHERMAN, M. S. (1952). *J. Bone Jt Surg.*, **34A**, 831. 7 figs, 12 refs.

The author, working at the University of Chicago, studied fifteen patients with psoriatic arthritis. She comments on the paucity in British and American literature of pathological studies of this condition. In this report she presents her conclusions, and gives the case histories in detail of seven of the patients. She claims that psoriatic arthritis is a definite clinical entity and should be distinguished from rheumatoid arthritis. In all the cases the joint changes were confined to the hands, wrists, and feet, with the major lesions in the more distal joints; there was always an asymmetrical pattern of involvement. None of the patients had fever, leucocytosis, lymphadenopathy, iritis, or subcutaneous nodules. Muscular atrophy and "rheumatoid" ulnar deviation of the hand were not seen. The disease progressed joint by joint, and only in the later stages was there a true polyarthritis.

Radiological changes were also characteristic. Bone atrophy was very slight, the earliest changes being in the interphalangeal joints, where marginal erosion occurred; later, gross destruction of bone took place. Bony ankylosis was seen in only two of the toe joints of one patient.

Biopsy material was obtained from 33 joints, and examined histologically. No characteristic pattern was seen; the findings varied greatly according to the evolutionary state of the lesion. In early lesions the synovial membrane was pale and oedematous, and the cartilaginous surfaces were normal. Later the inflamed synovial membrane eroded the edge of the articulating surface and the adjacent shaft. In the final stage the articulating ends were represented by stubs of cancellous bone embedded in fibrous tissue, with no trace of synovial membrane. Both the arthritic and, to a lesser degree, the cutaneous lesions responded temporarily to ACTH and cortisone.

On these clinical and radiological findings the author concludes that there is a type of chronic arthritis differing from rheumatoid arthritis to which patients with psoriasis are liable, but that the pathological changes are not characteristic. *K. C. Robinson.*

Sjögren's Syndrome. (Über das Sjögren Syndrom.) BEIGLBÖCK, W., and HOFF, H. (1952). *Dtsch. med. Wschr.*, **77**, 7 and 42. 1 table, 1 fig.

The authors conclude that Sjögren's syndrome is of rheumatic allergic aetiology, and that those organs are affected which are related to the metabolism of mucopolysaccharides. The syndrome manifests itself when the counteraction of cortisone or corpus luteum hormone are deficient. A patient with the syndrome was successfully treated with cortisone, ascorbic acid, and riboflavin. Implantation of pituitary glands was also successful. *W. Leydhecker.*

Sjögren's Syndrome treated with Cortisone. (Un caso de sindrome de Sjögren, tratado con cortisona.) MARANÓN, G., and FERNÁNDEZ, M. (1952). *Gac. méd. esp.*, **26**, 199.

A case of 10 years' duration in a 49-year-old woman with rheumatoid arthritis. The arthritis improved with systemic cortisone, but the influence of the hormone on the ocular condition is not mentioned. *Stewart Duke-Elder.*

Cortisone in the Treatment of Rheumatoid Arthritis in Children. MOWBRAY, J. (1952). *J. Irish med. Ass.*, **31**, 348. 15 refs.

Hydrocortisone in Rheumatoid Arthritis. BERRY, W. C., and BENSON, J. F. (1953). *U.S. armed Forces med. J.*, **4**, 99. 4 refs.

Management of Gold Therapy in Chronic Articular Rheumatism. (Die Durchfuhrung einer Goldbehandlung bei chronischrheumatischem Gelenkleiden.) HAPPEL, P., and MEYER, W. (1953). *Medizinische*, **6**, 175. 1 fig., bibl.

Gold Preparations in Rheumatoid Arthritis. KAIKINI, V. M. (1953). *Antiseptic*, **50**, 7.

Effect of Serum Hepatitis on Haemagglutination in Rheumatoid Arthritis. (Einfluss der Serümhepatitis auf die Hamagglutination bei chronescher Polyarthritis.) FERSTL, A. (1952). *Wien. Z. inn. Med.*, **33**, 532. 2 figs, 10 refs.

Response of Patients with Rheumatoid Arthritis to the Administration of Nitrogen Mustard. PHILLIPS, A. M., PHILLIPS, R. W., and CARAWAY, W. T. (1952). *R.I. med. J.*, **35**, 610. 7 figs, 25 refs.

Preliminary Report on the Use of Adrenergic Blocking Agents in the Treatment of Rheumatoid Arthritis. SCHATZBERG, M. (1952). *N.Y. St. J. Med.*, **52**, 2908. 2 refs.

Treatment of Rheumatoid Arthritis with Lyophilized Placenta. (Le Traitement de la polyarthrite chronique évolutive par le placenta lyophilisé.) COLINET, E., and BÖLCKE, R. (1952). *Acta physiother. rheum. belg.*, **7**, 247.

Surgical Therapy of Rheumatoid Arthritis. SHIMIZU, G. (1952). *Med. J. Osaka Univ.*, **3**, 165. 13 figs, 25 refs.

Clinical and Pathological Study of a Case of Felty's Syndrome with Splenectomy. (Étude clinique et anatomo-pathologique d'un cas de syndrome de Felty avec splénectomie.) BRUEGGER, Y. (1952). *Helv. med. Acta*, **19**, 501. 5 figs, bibl.

Poliomyelitis, with Myocarditis, complicating Still's Disease. PUGH, R. C. B. (1952). *Gt. Ormond Str. J.*, **4**, 118. 5 figs, 20 refs.

Heart in Cases of Rheumatoid Arthritis. An Electrocardiographic Investigation. ROHLIN, S., and SUNDELIN, F. (1952). *Cardiologia, Basel*, **21**, 470. 19 refs.

Treatment of Rheumatoid Arthritis. (Contribución al tratamiento de la artritis rheumatoide.) PÉREZ, J. P. (1953). *Clin. y Lab.*, **55**, 12.

Present-day Concept of Rheumatoid Arthritis and Allied Diseases. RAMOS, J. M. (1952). *R.I. med. J.*, **35**, 597. 9 refs.

Morbidity of Rheumatoid Arthritis. (Morbiditeten ved polyarthritis chronica promaria.) AMMITZBOLL, F., and SNORRASON, E. (1952). *Nord. Med.*, **48**, 1701. 9 refs.

Rehabilitation of the Rheumatoid Arthritic Patient. GILLMOR, C. S. (1952). *J. Mo. med. Ass.*, **49**, 976. 37 refs.

(Osteo-Arthritis)

Management of Osteo-Arthritis in the Aged. KUHNS, J. G. (1953). *J. Amer. med. Ass.*, **151**, 98. 4 figs, 12 refs.

Gonarthritis: a Common Form of Chronic Degenerative Rheumatism. (La Gonarthrie une forme frequente du rhumatisme chronique degeneratif.) FRANÇON, F. (1952). *Stetoscopio*, **2**, 117. 5 figs.

(Spondylitis)

Iritis complicating Ankylopoietic Spondylarthritis. [In Danish.] WESTERLUND, E. (1952). *Nord. Med.*, **48**, 1653.

(Miscellaneous)

Articular and Other Limb Changes in Acromegaly: a Clinical and Pathological Study of 25 Cases. KELLGREN, J. H., BALL, J., and TUTTON, G. K. (1952). *Quart. J. Med.*, **21**, 405. 15 figs, 38 refs.

The authors give a detailed report on the changes in the joints and other structures in 25 patients, nine male and sixteen female, suffering from acromegaly who were studied at the Rheumatism Centre, University of Manchester. They come to the conclusion that much of the pain in the back and limbs from which acromegalics suffer results from joint involvement which, they consider, is of a special type seen only in this disease. The most common changes in the joints were soft-tissue enlargement, synovial thickening, excessive and abnormal mobility, and recurrent effusions, and radiologically, increased joint space and remodelling of the ends of the bones. These changes were quite unlike those of osteo-arthritis or rheumatoid arthritis.

Of the authors' patients, three showed bilateral median-nerve involvement, which was due in one case to compression of the nerve and was subsequently relieved by operation. Thickening of the peripheral vessels was present in thirteen patients, and in the majority of cases over 40 years of age a significant degree of hypertension was found at out-patient examination. Histological studies indicated that the predominant change in the soft tissues was a non-inflammatory fibrous hyperplasia.

The authors compared the effect of hyaluronidase on the dispersal of physiological saline in the skin of twenty normal subjects and eleven acromegalics. They found that hyaluronidase was less effective as a spreading agent in the skin of acromegalic patients. It is suggested that this is due to some unknown qualitative change in the connective tissues. *D. G. Adamson.*

Radiological Diagnosis of Periarthrosis and Periarthritis. (Die Röntgendiagnostik der Periarthrose und der Periarthritis.) LEB, A. (1952). *Fortschr. Röntgenstr.*, **77**, 525. 9 figs, 33 refs.

Investigation of the periarticular soft tissues, which is essential for the radiological diagnosis of periarthrosis and periarthritis, may be accomplished in a number of ways. For the soft tissues to be visible on a plain radiograph the kilovoltage must be relatively high and the film slightly underexposed and underdeveloped so that the bone structure is just discernible. Contrast filling of the periarticular spaces, the synovial bursae, and the parafascial cells of the loose connective tissue is helpful, while the effect of periarthrotic processes on the articular space may be demonstrated by arthrography with a diodone preparation or by serial arteriography, which is useful also for the demonstration of periarticular ischaemia due to shrinking and fibrosis of the peri-

articular tissues. The rate of absorption of a water-soluble contrast medium injected into the joint may be determined as a means of estimating the efficiency of the periarticular lymphatic and vascular systems.

Where periarticular disease is present, the plain film shows a lack of definition and irregularity of outline of the soft tissues surrounding the joint. In cases of periarticular fibrosis or periarthrosis serial arteriography shows a deficient vascular network and the absorption of water-soluble media injected into the joint is delayed, whereas in acute periarthritis there is hyperaemia and absorption from the joint is accelerated. *A. Orley.*

Skeletal Changes in Cooley's Anaemia. (Le alterazioni scheletriche nel morbo di Cooley.) NAITANA, S. (1952). *Arch. Patol. clin. Med.*, **30**, 159. 30 figs, bibl.

This analysis of the skeletal changes in Cooley's anaemia is based on eleven cases studied at the universities of Bologna and Cagliari. Radiologically, the fundamental change common to all bones is rarefaction, with thinning of the corticalis, enlargement of medullary space, and absorption of trabeculae (with the exception of those carrying the chief stresses, which became more prominent), producing a sandy, porous, or "micro-areolar" appearance.

The skull shows frontal and parietal bossing, so that width and height are increased in relation to vertical height, and the vertex is flattened and sometimes depressed ("camel's back" appearance); the internal and external tables are thinned and may disappear, while radiating spicules of bone form perpendicular to the tables, particularly near the sutures and fontanelles, which may show parallel transverse striations simulating an external table; ultimately the appearance is that of bristles radiating from a thinned internal table. The paranasal sinuses may show opacities due to osteophytes.

In the vertebral column abnormal trabeculation is usual, and may be mistaken for an angioma or, more rarely, for Paget's osteitis deformans; the transverse processes and the vertebral ends of the ribs are swollen and rarefied. The long bones sometimes show new bone formation in spicules perpendicular to the periosteum, so that the appearance is that of an osteogenic sarcoma; the epiphyses are often swollen and their union is delayed.

Anatomically, the skull is flat and the diploë thickened. The internal and external tables of the skull and the cortex of the long bones may be reduced to paper thinness. There appear to be coincidental endosteal absorption and periosteal growth of bone. The epiphyseal cartilages are transparent and mucoid. Pathological fractures are uncommon. *George Discombe.*

Paget's Disease (Osteitis Deformans). Review of One Hundred and Eleven Cases. ROSENKRANTZ, J. A., WOLF, J., and KAICHER, J. J. (1952). *Arch. intern. Med.*, **90**, 610. 4 figs, bibl.

The authors review the findings in 111 cases of Paget's disease admitted to the Veterans Administration Hospital, Bronx, New York, between 1941 and 1950, and discuss theories of causation and methods of treatment. They point out that alkaline phosphatase is essential to bone growth and repair. The serum alkaline-phosphatase level was normal in 23 out of 74 cases in which it was estimated, three different techniques being used. When the degree of bone involvement was correlated with the serum alkaline-phosphatase level, it was found that with increased bone involvement there was a rise in the serum alkaline-phosphatase level. Of five cases in which there were sarcomatous changes the alkaline-phosphatase level was normal in two, slightly raised in two, and markedly raised in one. The serum cholesterol and total protein concentrations were within normal limits; the basal metabolic rate, which was determined in eleven patients, was also within normal limits. The 17-ketosteroid excretion was below normal in two out of eight patients.

Like other observers, the authors noted that Paget's disease was often an unexpected finding during *x*-ray examination. The pelvic bones were most often affected, followed by the skull and then the femur. The bone least often affected was the mandible, there being only one case of osteitis deformans of the mandible in the present series. Among the complications were chronic arthritis (38 cases), salivary calculi (twenty cases), pathological fractures (seventeen cases), sarcomatous changes (eight cases), and multiple myeloma (one case). The authors list a number of remedies which have been advocated in the past and dismiss them all as useless. Administration of corticotrophin caused an initial fall in the serum alkaline-phosphatase level in two cases, but this was followed by a return to the pre-treatment level. In both cases there was subjective improvement with relief of bone pain; in one case the hormone caused congestive failure and had to be withdrawn. *William Hughes.*

Acute Haematogenous Osteitis in Childhood. A Review of 212 Cases. WHITE, M., and DENNISON, W. M. (1952). *J. Bone Jt Surg.*, **34B**, 608. 15 figs, bibl.

This review of treatment in a series of 212 cases of osteomyelitis in children admitted to the Royal Hospital for Sick Children, Glasgow, during the 15 years from 1936 to 1950 falls naturally into three periods marked by the introduction of sulphonamides in 1941, and of penicillin in 1945.

In the first period (1936-40) 75 patients were treated, with a mortality of 36 per cent. Blood culture was positive in 50 per cent. of cases before treatment and was usually negative after the 9th day in the survivors. The organism involved was *Staphylococcus aureus* in 95 per cent., a streptococcus in three, and a pneumococcus in one. The onset of pain was 1 to 10 days before admission. Of the 27 fatal cases, in thirteen the patient died within 5 days of admission. Treatment during this period was surgical according to the principles of Winnet Orr. Infective arthritis occurred as a complication in two cases and overgrowth of bone in seven. Pathological fracture was common.

During the second period (1941-45) 55 patients were treated, with a mortality of 12·7 per cent. The clinical

features and bacteriology of these cases were similar to those of the first group and similar surgical methods of treatment were used, but were now combined with the administration of sulphathiazole. The duration of fever was shorter and metastases fewer, but healing was no more rapid and the degree of bone destruction much the same as without sulphathiazole. Only nineteen patients were followed up in this group, ten of whom had developed some complication such as overgrowth of bone, adherent scar, sequestrum formation, or ankylosis of a joint.

During the third period (1946-50) 82 cases were treated, with a mortality of only 1·2 per cent. The bacteriology was similar to that of the first two groups, but in two cases penicillin-resistant staphylococci were found. The response of the septicaemia to penicillin was dramatic, the blood culture, if positive on admission, being negative by the 3rd day in all but the two cases mentioned above. In over 80 per cent. of cases pus was present on admission. Neither the temperature nor the leucocyte count could be regarded as good guides to the progress of the bone disease under treatment with penicillin, careful examination and repeated marrow aspiration and radiography being required, though early treatment with penicillin may so inhibit the disease that radiological changes may never be seen. Pyogenic arthritis was present in twelve cases and was treated by aspiration and the instillation of penicillin, with recovery of movement in nine cases, gross epiphyseal damage in two, and bony ankylosis in one. Limb overgrowth occurred in thirteen cases, pathological fracture in seven cases, and sequestra needed removal in fourteen cases.

Current methods of treatment are directed towards the control of septicaemia and the reduction of tension in the bone focus. Except for patients under 3 months of age, for whom aureomycin by mouth is preferable, penicillin is given to all patients up to the age of 5 years by intramuscular injection at 3-hourly intervals in doses varying from 80,000 to 200,000 units. However, "once an abscess has formed it cannot be sterilized by the systemic administration of penicillin, and in such cases surgery is still necessary". Aspiration is unsatisfactory, bone drilling is seldom necessary, and guttering and saucerization "have no place in the modern treatment of osteitis". Incision of the abscess followed by primary suture is considered to be the best line of treatment.

[This article gives a summary of the present state of treatment of osteomyelitis with which most orthopaedic surgeons would be in agreement. An additional argument in favour of incision and primary suture and against aspiration is that the incision gives time for further exudate to escape from the cavity walls as they collapse. It is disappointing to note that the disease is not being diagnosed at an earlier stage before admission to hospital, in spite of the widespread interest and publicity given by the dramatic response of osteomyelitis to antibiotics. It is to be hoped that these are not dulling the sense of alarm which the condition used to arouse in the past, for the statistics quoted in this article show that a considerable number of complications still occur in spite of adequate treatment.] *J. G. Bonnin.*

Arthritic and Rheumatoid Complications of the Treatment of Thyrotoxicosis with Radioactive Iodine (^{131}I). (Über arthritische und rheumatoide Erscheinungen bei radiojodidbehandelten (J^{131}) Thyreotoxikosen). PRÉVÔT, R., and HORST, W. (1952). *Strahlentherapie*, **88**, 253. 20 refs.

The authors report a series of 100 cases of thyrotoxicosis treated with radioactive iodine (^{131}I) at the University Hospital, Hamburg. There were thirteen male and 87 female patients; seventy had been treated unsuccessfully by surgery or with *x* rays or drugs, the remaining thirty patients having received no previous treatment. In all, 243 treatments with ^{131}I (as potassium iodide) were given, to total dosage ranging from 6,000 to 30,000 roentgen equivalents per gramme of thyroid tissue. Satisfactory results (disappearance of goitre, return of the basal metabolic rate and pulse rate to normal or near normal levels) were obtained with one treatment in 32 patients, with two treatments in 28 patients, and with three or more treatments in 32 patients. In the remaining eight patients limited improvement only was obtained, and further treatment is planned.

The authors analyse the risks and complications of treatment with ^{131}I. The mortality in their series, as in other reported series, was *nil*, compared with an average of 2 per cent. after thyroidectomy. The risk from the carcinogenic effects of radiation has been shown by experiments on animals to be minimal, and compares favourably with the risk of operative death. Similarly, the chances of inducing myxoedema with ^{131}I are no greater than with thyroidectomy, in which there is the additional risk of operative injury to the parathyroid glands or to the recurrent laryngeal nerve. In the authors' series exacerbation of the symptoms of thyrotoxicosis occurred in 8 cases, but lasted a few weeks only and was well controlled by small doses of potassium iodide. One patient developed myxoedema, and two others transient thyroid deficiency. Arthritic or rheumatoid complications, including periarthritis of the shoulder joint, lumbago, osteo-arthritic changes, and polyarthritic symptoms, occurred in 10 cases. These symptoms could not be regarded as due to thyroid deficiency, as thyroid function in these cases was at the upper limit of normal. In seven cases they disappeared in a few weeks with physiotherapy and anti-rheumatic drugs, but in the other three they persisted.

In discussing the cause of this complication the authors draw attention to the physiological interrelationship between the thyroid gland and the adrenal cortex, the latter having an inhibitory influence on thyroid function. They regard the condition as a manifestation of Selye's "disorder of adaptation", but do not consider its occurrence a contra-indication to the treatment of hyperthyroidism with ^{131}I. However, they recommend the use of a fractionated dosage of radiation, and recommend that thyroid activity be reduced only to the upper limit of normal. *L. G. Capra.*

Benefits and Toxicity of Phenylbutazone ("Butazolidin") in Rheumatoid Arthritis. STEPHENS, C. A. L., YEOMAN, E. E., HOLBROOK, W. P., HILL, D. F., and GOODIN, W. L. (1952). *J. Amer. med. Ass.*, **150**, 1084. 3 refs.

The authors have used phenylbutazone ("Butazolidin") in the treatment of 188 patients, of whom 147 had

rheumatoid arthritis or ankylosing spondylitis, at the Southwestern Clinic, Tucson, Arizona. The average duration of treatment was 85 days, but 36 patients were treated for 150 to 455 days. The daily dose ranged from 200 to 1,600 mg. [average 600 mg.], given by mouth in divided doses. As 44 per cent. of the patients suffered from toxic effects, consisting principally of reduction in platelet count and haemoglobin level, gastric irritation, skin rashes, and haematuria, it was concluded that the drug is by no means innocuous.

Striking subjective improvement was obtained in a high proportion of the patients with spondylitis, but treatment was less effective in rheumatoid arthritis. Objective improvement was less striking but was, in the authors' opinion, definite in a small percentage of cases. While they are unable to decide whether the drug is truly anti-rheumatic or only analgesic, they consider it to be worthy of further study on a wider scale.

W. S. C. Copeman.

Observations on the Use of "Butazolidin" in Arthritis. DAVIES, H. R., BARTER, R. W., GEE, A., and HIRSON, C. (1952). *Brit. med. J.*, **2**, 1392. 1 fig., 6 refs.

The authors describe the results of treatment of one hundred patients, many of them suffering from rheumatoid arthritis, with Butazolidin (phenylbutazone), a drug recognized as having analgesic and antipyretic properties. Patients were examined before, and again 4 weeks after, treatment. One group of patients were given phenylbutazone and another, comparable, group received injections of saline; neither patient nor physician knew to which series a particular patient belonged. The drug was given by injection, starting at 1 g. per day and slowly decreasing the dosage. Latterly it has been given by mouth. Progress was assessed by measurement of joint temperature, grip, and a timed action. More improvement seemed to be shown in the treated than in the control cases. In some patients with osteo-arthritis of the hip a very good analgesic effect was noted. In all cases the temperature became normal, while the erythrocyte sedimentation rate was unaffected. Adverse effects were pain at the site of the injection, gastro-intestinal disturbance, water retention, rash, and purpura. Symptoms returned 3 to 7 days after cessation of treatment.

[The records as published are inadequate for assessment of the effect of treatment—especially in rheumatoid arthritis, a disease in which the results of treatment are notoriously difficult to evaluate.] *G. Loewi.*

Some Pharmacological Aspects of Phenylbutazone ("Butazolidin"), a New Antirheumatic. DOMENJOZ, E. (1952). *Int. Rec. Med.*, **165**, 467. 9 figs, 11 refs.

In this paper from the University of the Saar, Saarbrücken, the author discusses the pharmacological properties of phenylbutazone, which has been found to produce good effects in the treatment of rheumatic disorders, without the undesirable central effects caused by large doses of aminopyrine. Although chemically the drug is diphenyl-dioxo-butylpyrazolidine, it differs in constitution and physico-chemical properties from other pyrazole compounds hitherto used in therapeutics. Its clinical efficacy seems to depend on three properties, namely, its analgesic, antipyretic, and anti-inflammatory action.

Experiments in rabbits showed that phenylbutazone is eliminated more slowly than aminopyrine. When 100 mg. of each drug per kg. body weight was given to these animals and the blood level determined over a period of 24 hours, it was found that the aminopyrine had been completely eliminated in 13 hours but the phenylbutazone persisted for 24 hours. The analgesic properties of the drug were compared with those of morphine by measuring the threshold for electrical stimulation of the dental pulp. The intravenous injection of 100 mg. phenylbutazone per kg. body weight raised the threshold by approximately 50 per cent., whereas a dose of 2 mg. morphine hydrochloride per kg. raised it by 65 per cent. Phenylbutazone was shown to have an antipyretic effect of equal magnitude but of longer duration than that of phenazone.

In further experiments plethysmographic measurements of the volume of the rat's foot showed that 200 mg. phenylbutazone per kg. body weight injected subcutaneously reduced the degree of oedema normally produced by an injection of egg albumen. Oedema induced in the rat's foot by formalin was similarly inhibited. Phenylbutazone was also found to antagonize the effects of histamine on the perfused rabbit's ear, and to increase the lethal dose of histamine in guinea-pigs. On the other hand, it did not readily inhibit the effects of histamine on the isolated gut or on the blood pressure.

[The number of animals used is given for only some of the experiments described in this paper. Even where the number is stated no indication is given of the variation in the results, and it is, therefore, difficult to assess their validity.] *P. A. Nasmyth.*

Phenylbutazone Therapy of Arthritis and other Painful Musculoskeletal Disorders. STEINBROCKER, O., BERKOWITZ, S., EHRLICH, M., ELKIND, M., and CARP, S. (1952). *J. Amer. med. Ass.*, **150**, 1087. 4 refs.

Phenylbutazone ("Butazolidin") was administered to 52 patients with painful musculo-skeletal disorders at the Hospital for Joint Diseases and Lenox Hill Hospital, New York, in an average dosage of 600 mg. daily by mouth. As a result of their observation of these cases the authors consider that as an analgesic in such conditions this new drug is appreciably more effective than salicylates, sodium gentisate, and amidopyrine. They state that they could also detect evidence of an anti-arthritic effect in rather less than one-quarter of their patients, this being more noticeable in ankylosing spondylitis and osteo-arthritis than in rheumatoid arthritis. Toxic effects occurred in 25 per cent. of the cases treated, though none was serious. It was deemed advisable, however, to suspend treatment in 22 of the cases. The therapeutic effect was obtained soon after administration of the drug and wore off rapidly on cessation of treatment. There appeared to be no effect on erythrocyte sedimentation rate or the number of circulating eosinophils.

The authors conclude that phenylbutazone is a useful analgesic in rheumatic conditions, but that the dangers

inherent in long-term administration should become the subject of large-scale investigation. *W. S. C. Copeman.*

Tocopherol Administration to Patients with Dupuytren's Contracture. Effect on Plasma Tocopherol Levels and Degree of Contracture. KIRK, J. E., and CHIEFFI, M. (1952). *Proc. Soc. exp. Biol., N.Y.*, **80**, 565. 1 fig., 8 refs.

The favourable effects of tocopherol (vitamin E) in cases of Dupuytren's contracture were first reported by Steinberg (*Med. Clin. N. Amer.*, 1946, **30**, 221). Since then conflicting reports on its value have appeared. The present investigation was carried out at the St. Louis City Infirmary Hospital (Washington University School of Medicine), on 26 contracted hands in fourteen men and five women whose mean age was 74 years. A daily dose of 300 mg. of DL-alpha-tocopherol acetate was given for 300 days and the patients were kept under observation for a further 350 days.

The degree of contracture was measured by means of plaster casts of the hands made under standard conditions. Two measurements were chosen—the degree of concavity of the palm, and the angle between the fifth finger and the direction of the palm. The latter was measured directly, the former indirectly by filling the palm with sand and measuring its cubic capacity. The average plasma tocopherol level before treatment was 0·55 mg. per 100 ml. compared with a mean normal value of 1·02 mg. per 100 ml. previously determined for this age group. After 300 days' treatment the mean value had risen to 1·37 mg. per 100 ml., and 215 days after stopping treatment it had returned to its original level.

In no case of moderately severe contracture did the treatment result in disappearance of the extension defect of the fingers. However, a definite improvement was noted, and in 23 of the 26 cases the palmar concavity became less marked, although on the whole this moderate degree of objective improvement was not noticed by the senile patients. These findings thus support the contention that tocopherol has a beneficial effect on Dupuytren's contracture, though the response was limited; this may have been due to the advanced age of the patients, as Thomson (*Brit. med. J.*, 1949, **2**, 1382) has reported much better results in younger patients with disappearance of the contracture in some cases.

[It appears that there may be two or more responsible factors in the causation of Dupuytren's contracture. In the senile patient and the patient with coronary thrombosis who develops the lesion in the left hand the cause appears to be vascular, which may explain the limited response in elderly patients with an avascular, fibrous palm. An investigation of a group of younger patients, carried out with the same accuracy as that reported here, is still required to establish the claims for the efficacy of tocopherol therapy, which most observers of limited numbers of cases consider to have been overstated.]

J. G. Bonnin.

Rehabilitation of the Disabled Housewife. COOKSEY, F. S. (1952). *Ann. phys. Med.*, **1**, 120. 4 figs.

Much progress has been made in the rehabilitation, vocational training, and resettlement of the handicapped child and industrial worker, but little has been done to help the disabled housewife, whose work "is one of the most important industries in the country". The author outlines a plan for adoption by departments of physical medicine in retraining the disabled housewife. The ordinary activities of daily life, such as dressing and feeding, are practised in the department under supervision, with adaptation of clothing and the use of special appliances when necessary. Later, domestic retraining is given with the aid of a special kitchen unit so designed that it can be adjusted to the patient's disability. The unit which is in use at King's College Hospital, London, is described in full. Retraining includes cooking, the most essential domestic duty, washing and ironing, and (especially for people living alone) bed-making. It is suggested that coal fires should be replaced by gas or electric fires and that cleaning should be left to the domestic help. The occupational therapist visits the patient's home to offer advice on the alterations needed, and the almoner secures the help as needed of the landlord, local authority, or hospital workshop in carrying them out.

The plan enables the physical medicine department to co-operate with the welfare department and the voluntary associations in rehabilitating the disabled housewife.

M. H. L. Desmarais.

Aspects of the Urethritis-Conjunctivitis-Arthritis Triad. (Aspects actuels de la triade urétrite-conjonctivite-arthrite.) DAGUET, G. (1952). *Ann. Derm. Syph. Paris*, **79**, 149. Bibl.

The subject is exhaustively reviewed and particular attention is paid to clinical manifestations and the organisms which have been held to be responsible for the syndrome. *S. J. H. Miller.*

Erythema Multiforme Exudativum. Study of Fifteen Cases. BILLOW, B. W., and LOWEN, H. J. (1952). *Arch. intern. Med.*, **90**, 310. 3 figs, 22 refs.

The authors trace the history of erythema multiforme exudativum from the original description by Hebra in 1860 to the present time, and discuss the various theories of causation, the clinical findings, and the treatment which have been reported in the literature.

They analyse, in a table, the history, diagnostic signs, and clinical features in fifteen personal cases. The most frequent, and specific, diagnostic signs were the toxic appearance of the patient, lesions of the eye and mucous membranes, and a maculo-papular, vesicobullous, haemorrhagic skin rash. Less frequent, but equally important, signs were pneumonitis, sore throat, malaise, joint pains, and erythema nodosum. Two of their cases in which there was hypersensitivity to drugs were indistinguishable clinically from the other thirteen in which the cause was attributed to an infectious agent of unknown origin. Pathological and biochemical investigations did not reveal anything of note. Aureomycin and penicillin were useful in controlling secondary infection, but the authors doubt whether they have any specific action.

The authors suggest that the term erythema multiforme exudativum should be used to denote a recognized

entity, rather than the eponyms Stevens-Johnson syndrome, Behçet's disease, and Hebra's disease.
G. B. Mitchell-Heggs.

Unusual Reaction following Use of Phenylbutazone. Report of a Case. CHARET, R., and SIEGEL, I. (1953). *J. Amer. med. Ass.*, **151**, 556. 1 fig., 2 refs.

Phenylbutazone, which is used in the treatment of arthritis may have undesirable side reactions. Among them, as is described in a case reported in this paper, are skin eruptions and photophobia, with redness of the conjunctiva. Treatment was undertaken with ACTH, penicillin, and aureomycin, and the condition cleared rapidly. *A. G. Cross.*

Balanitis Circinata in Reiter's Disease. Symptoms and Histology. (Balanitis circinata bei Reiterscher Krankheit. Klinik und Histologie.) REICH, H. (1952). *Arch. Derm. Syph. Berl.*, **194**, 1.

Description of the histology and clinical picture of balanitis in Reiter's syndrome. *W. Leydhecker.*

The Treatment of Reiter's Disease with Threomycin. [In Hungarian.] NAGYVÁRADI, J. (1953). *Orv. Het. (Hung. med. Weekly J.)*, **94**, 106.

The author discusses in detail the aetiology of Reiter's disease, which is not yet clear. In the case discussed gonorrhoea and dysentery were definitely excluded. His opinion is that the morbid principle is a virus and an important condition to the outbreak of the infection is the preliminary diminishing of the organism. After treatment with 20 g. threomycin improvement appeared.
P. Weinstein.

A Case of Behçet's Syndrome. (Um caso de sindroma de Behçet.) FONSECA, F., BRANCA, F., PINA, A., and GANDER, G. (1952). *Clin. Contemp., Lisboa*, **6**, 36.

Report of a case in a 22-year-old female with recurrent aphthous stomatitis, nodular cutaneous lesions with pain in the inferior members, vaginal discharge, and bilateral iritis. The biopsy of a cutaneous nodule showed normal epidermis, granuloma in the dermis and hypodermis, many histiocytes, lymphocytes, neutrophil polynuclears, some eosinophils, and giant cells similar to those of erythema exudativum multiforme. In several places there were perivascular nodules similar to erythema nodosum. Cortisone, systemic and local, reduced the frequency and intensity of the muco-cutaneous attacks considerably, and cured the iritis (some synechiae remaining only and visual acuity about 0·8).

For 8 months, without any treatment, the patient has continued well. *P. Moutinho.*

Behçet's Disease. KARANI, S. B. (1953). *Proc. roy. Soc. Med.*, **46**, 45. 2 figs, 3 refs.

A man aged 24 was treated with antibiotics, cortisone (locally for eyes), ACTH, anti-coagulant, and testosterone without effect. *A. G. Leigh.*

Butazolidin in the Treatment of Rheumatism. (Butazolidin als Antirheumatikum.) BELART, W. (1953). *Dtsch. med. Wschr.*, **78**, 129. 5 refs.

Clinical Evaluation of Phenylbutazone. PATTERSON, R. M., BENSON, J. F., and SCHOENBERG, P. J. (1953). *U.S. armed Forces med. J.*, **4**, 109. 5 refs.

Effect of L-Cysteine Hydrochloride, DL-Alanine, Hydrochloric Acid and Sodium Hydrosulfide on Experimental Polyarthritis of Rats. LIBENSON, L., and WETZEL, V. (1952). *J. infect. Dis.*, **91**, 216. 3 figs, 11 refs.

Diagnostic Helps in Rheumatic Diseases. MARTIN, W. J. (1953). *Med. Ann. Distr. Columbia*, **21**, 661.

Butazolidin in Rheumatic Diseases. GOLDFAIN, E. (1953). *J. Okla. med. Ass.*, **46**, 27. 6 refs.

Disk Syndrome

Tables for Vertebral Elongation in the Treatment of Sciatica. NEUWIRTH, E., HILDE, W., and CAMPBELL, R. (1952). *Arch. phys. Med.*, **33**, 455. 3 figs, 3 refs.

The authors report from the U.S. Veterans Administration Center, Whipple, Arizona, on the treatment of sciatica caused by disk protrusion by means of the vertebral elongation technique, for which they use a modification of Godet's table. They regard it as essential that conditions other than disk protrusion be excluded before this treatment is instituted. When there is no absolute indication for surgery, they recommend that elongation of the lumbar segment of the vertebral column should be tried, this method being applicable to both acute and chronic cases. In chronic sciatica, if there has been no improvement after 6 treatments, they advise the discontinuance of this therapy.

The main mechanical effects of the treatment are to widen the intervertebral and apophyseal spaces and to stretch ligaments, muscles, and adhesions. The treatment also tends to reproduce the anatomical and physiological conditions that existed before the development of sciatica.

The authors report the results of treating thirteen patients with sciatica by their method, eight of whom were cured, three improved, and two failed to respond. They conclude that the best results with this technique are obtained by its combination with sleeping on a firm mattress and the wearing of a low back support.
M. H. L. Desmarais.

Neurological Manifestations of Cervical Spondylosis. BRAIN, W. R., NORTHFIELD, D., and WILKINSON, M. (1952). *Brain*, **75**, 187. 16 figs, 38 refs.

Attention is drawn to the importance of cervical spondylosis as a cause of alteration of function in the cervical segments of the spinal cord, this conclusion being based on 45 cases of cervical spondylosis seen at the London Hospital. In 38 of these patients there was unequivocal evidence of spinal-cord disorder, and in six necropsy had been performed. The disability is usually slowly progressive for one or two years and may then remain stationary for long periods. The neurological disturbance varies a good deal, but commonly there is pyramidal involvement affecting the arms

and legs and often impairment of position sense, especially in the hands, with variable cutaneous sensory disturbance. The Queckenstedt response is frequently normal, and the only common abnormality in the cerebrospinal fluid is some increase in protein content, the highest value found in this series being 160 mg. per 100 ml.

In these cases the most important investigation is radiography of the cervical spine, the most common findings being narrowing of one or more intervertebral-disk spaces, anterior and posterior osteophytes on the vertebral bodies, abnormalities in the articular surfaces of the neuro-central joints, and projection of osteophytes into the intervertebral foramina. Conservative treatment consists in immobilization of the cervical spine, with physiotherapy for the limbs; in cases treated early enough satisfactory improvement in symptoms may occur. Operative treatment consists in laminectomy, "unroofing" of the intervertebral foramina, and opening of the dura and division of the denticulate ligament with the object of giving greater mobility to the spinal cord and relieving pressure on the nerve roots. Operation was performed on 21 patients, and the best results were obtained in the younger patients with a short history.

The literature is extensively reviewed, detailed histories of the six patients coming to necropsy are given, and the paper includes a discussion on the mechanism of the damage to the spinal cord. *J. W. Aldren Turner.*

Discography. Technique, Indications, and Evaluation of the Normal and Abnormal Intervertebral Disc. CLOWARD, R. B., and BUZAID, L. L. (1952). *Amer. J. Roentgenol.*, **68**, 552. 10 figs.

Cervical Spondylosis. Clinical and X-ray Investigation. (Cervikalspondylose. En klinisk og rontgenologisk undersokelse.) BORMER, T., and EVANG, E. (1952). *Nord. Med.*, **48**, 1330. 4 figs, 25 refs.

Gout

Therapeutic Value of Probenecid (Benemid) in Gout. PASCALE, L. R., DUBLIN, A., and HOFFMAN, W. S. (1952). *J. Amer. med. Ass.*, **149**, 1188. 5 figs, 19 refs.

Since probenecid-p(di-n-propylsulfanyl)benzoic acid is capable of blocking tubular reabsorption, the authors have tried the therapeutic effect of this product in gout. In all, twenty patients were studied, five very completely. All subjects treated were placed on a low purine diet and varying methods of dosage were employed, 0·5 g. every 6 hours, 2 g. every other day, and 2 g. on successive days each week. A prompt reduction in the serum urate concentration occurred in fourteen patients, a more gradual fall over 96-120 hours in three, and no decrease in the remaining three, all of whom had associated renal insufficiency. The patients treated with 2 g. on the first 2 days of the week continued to show prompt falls in the serum uric acid level and there was no evidence of refractoriness to the drug. One or more acute attacks occurred in nine patients during treatment. Without the additional therapeutic aid of ACTH or colchicine the attacks were prolonged, some lasting 12 days. Acetyl salicylic acid, given in doses of 1-3 g. over 6 hours, completely suppressed the action of probenecid, presumably by blocking its uricosuric action.

The authors compare and contrast the action of salicylates and probenecid and suggest that it produces its blocking action of urate reabsorption only if it is conjugated in the tubular cell, the negativizing action of salicylates being due to the latter competing in the tubules with probenecid for the conjugating enzymes.

The authors discuss the failure to prevent acute attacks and the apparent slowness of action upon tophi, but consider that the evidence justifies the use of the drug for long-term therapy. The only serious toxic manifestation which followed its use was one instance of haematuria. Liberal supplies of fluid and alkalies are recommended to minimize the possibility of such a complication. *R. E. Tunbridge.*

Corticotrophin and Cortisone in the Treatment of Chronic Gout. (ACTH et cortisone dans le traitement de la goutte chronique.) COSTE, F., PIGUET, B., DELBARRE, F., and FRÉZAL, J. (1952). *Ann. Méd.*, **53**, 647. 10 figs, 17 refs.

The authors record their results in twelve patients suffering from severe chronic polyarticular gout who were treated at the Hôpital Cochin, Paris, with corticotrophin (ACTH) or cortisone or both; these patients had proved to be resistant to colchicine and salicylates. The dosage and duration depended on the severity of the condition and the response; the usual dose of cortisone was 100 mg. daily, given by intramuscular injection, and the total dose of ACTH averaged 1·5 g., and that of cortisone 4 g. The patients were kept on a purine-free diet and were deprived of alcohol. A rapid remission of symptoms was observed in seven out of nine cases of chronic tophaceous gout treated with ACTH or cortisone or both, in one out of two cases of chronic non-tophaceous gout treated with ACTH, and in one case of recurrent gout treated with ACTH; the mobility of stiff joints was improved in the cases which responded, and in five cases a "modest regression" of the tophi was observed. No adverse effects from the drugs were observed. The clinical improvement has been maintained in six cases for a period of many months.

The eosinophil response to a test dose of ACTH given before treatment showed the characteristic sharp fall in eosinophils (Thorn's test). The plasma uric acid content was significantly decreased during five out of nine courses of treatment with ACTH, and during two out of five courses of cortisone; the urinary excretion of uric acid showed increased values during eight out of nine periods of treatment with ACTH, and during three out of five with cortisone. The authors relate these findings to a progressive reduction of the "miscible pool" of uric acid.

They conclude that ACTH and cortisone are likely to be useful in the treatment of exacerbations of chronic gouty arthritis in patients who have proved resistant to

the usual treatment. They note that in several of the cases one or more exacerbations occurred towards the end, or soon after the cessation, of treatment with ACTH, but it was found that these attacks usually responded well to colchicine, although this drug had previously proved ineffective, and they recommend [apparently on the basis of this latter finding] treatment by alternating the several drugs, old and new, which are known to be of value in gouty arthritis. *Joseph Parness.*

Non-Articular Rheumatism

Procaine and Procaine Amide Hydrochloride in Skeletal Pain. TRAUT, E. F. (1952). *J. Amer. med. Ass.*, **150**, 785. 2 refs.

The effects of procaine hydrochloride and procaine amide hydrochloride in relieving pain in various joint diseases and other skeletal conditions were compared at the Presbyterian and Cook County Hospitals, Chicago. The latter drug was ineffective when given by mouth in doses of 3 g. daily for a week, while a similar dose of procaine hydrochloride gave only doubtful relief. Given intravenously, procaine amide was ineffective in three cases of skeletal carcinomatosis and three of rheumatoid arthritis. On intradermal injection, procaine amide hydrochloride produced analgesia more slowly than procaine hydrochloride (1 to 4 min.), but lasting no longer and no more effective. A dose of 10 to 60 ml. 1 per cent. procaine amide solution, given by periarticular + intra-articular injection, gave prompt and lasting relief in degenerative arthritis; equally good results were given by periarticular infiltration alone, whereas intra-articular injection alone gave prompt but transient relief, which was no different from that given by procaine or by saline. Slighter and more transient relief was given by infiltration with procaine amide in rheumatoid arthritis, but intra-articular injection gave none. In cases of radiculitis due to pressure or postherpetic neuralgia prompt and lasting benefit was obtained by infiltration of the nerve roots with procaine amide. The drug was also used successfully for the injection of fibrositic nodules in the back and for the infiltration of painful bursae and tendon sheaths around the shoulder. The "shoulder-hand syndrome" was promptly relieved by infiltration of the stellate ganglion, which did not result in a Horner's syndrome as would have been the case with procaine.

The side-effects of procaine amide hydrochloride were negligible. There was no nausea, giddiness, or vomiting and no effect on the blood picture, erythrocyte sedimentation rate, or electrocardiogram. The authors have abandoned as unnecessary the premedication of their patients before injection. On account of its low toxicity, they consider procaine amide superior to procaine for the infiltration treatment of painful skeletal conditions.

Stephen G. Gang.

Fibrositis in Industry and the Laughton-Scott Technique. HEALD, C. B. (1952). *Trans. Ass. industr. med. Offrs.*, **2**, 106. 5 refs.

General Pathology

Iron Absorption Tests in Anaemia: the Use of Intravenous Iron Preparations. CRAWLEY, J. (1952). *Edinb. med. J.*, **59**, 478. 1 fig., 15 refs.

The absorption of iron given intravenously was examined in patients with iron-deficiency anaemia who had failed to respond to prolonged courses of iron by mouth.

Iron absorption tests were performed on six normal subjects, 34 patients with hypochromic anaemia who subsequently responded to oral iron therapy, and five patients with hypochromic anaemic refractory to orally administered iron preparations. From the tests it appears that refractoriness to oral iron therapy is related to a failure of iron absorption, and in patients in whom this was found the iron absorption curve was of the flat type. Intravenously administered iron was not excreted in the faeces, but there was a urinary iron output of about 4 per cent.

The author concludes that there is a definite place for parenteral iron therapy in some patients suffering from persistent gastro-intestinal disturbances, particularly during pregnancy, in cases of rheumatoid arthritis, and in patients suffering from gross external blood loss; also where there is inadequate absorption of iron in patients with persistent diarrhoea after resection of parts of the intestinal tract.

John F. Wilkinson.

Basis of the Erythrocyte Sedimentation Rate. HARDWICKE, J., and SQUIRE, J. R. (1952). *Clin. Sci.*, **11**, 333. 4 figs, 25 refs.

In artificial systems a function of the "corrected" maximum rate of sedimentation has been shown to bear a linear relation to the concentration of macromolecules added. The degree of effect varies with different macromolecules, increasing with molecular size. This function applies to all the colloids examined, namely, dextrans, gelatin, gum acacia, polyvinyl pyrrolidone, and fibrinogen. To demonstrate this effect, maximum sedimentation velocities are determined at standard cell concentration, and "corrections" applied for viscosity of suspending fluid, and for fluid and red cell specific gravities.

In a series of normal and diseased persons the difference between this function of the plasma and serum sedimentation rates is shown to depend directly on the plasma fibrinogen concentration. Elevated fibrinogen values do not account completely for the rise of sedimentation rate in disease. The serum sedimentation rate is shown to be associated with the concentrations of α_2 and γ globulins, as estimated by electrophoresis on filter paper. Variations in these components may have diagnostic significance, and merit further investigation.

The limitations of routine methods of estimating the ESR are demonstrated. The practical value of determination of plasma and serum viscosity is discussed, since variations in these values appear to depend largely on plasma protein changes similar to those concerned in erythrocyte sedimentation.—[*Authors' summary.*]

Relation between Joint Stiffness upon Exposure to Cold and the Characteristics of Synovial Fluid. HUNTER, J., KERR, E. H., and WHILLANS, M. G. (1952). *Canad. J. med. Sci.*, **30**, 367. 9 figs, 14 refs.

In this paper from the Defence Research Laboratories Toronto, on the effect of cold on joint movement, four groups of experiments are described:

(A) The speed of flexion at the proximal interphalangeal joint of the index finger of twelve subjects was measured before and after exposure to cold. For this purpose two push-buttons were used, each operating a counter and separated by a baffle so that the finger must be flexed in moving from one to the other. The number of contacts made with each button in turn during a period of 10 sec. provided a measure of flexion speed.

(B) Radiographic records of the movements at the proximal interphalangeal and knee-joints were studied to determine the type of movement involved.

(C) The increase in viscosity with fall in temperature of various specimens of bovine synovial fluid was determined and its relation to the mucin content studied.

(D) Movement of the cat's knee-joint was studied *in vivo*, the tension exerted through the patellar ligament to produce different rates of shear being studied in relation to the characteristics of synovial fluid as determined *in vitro*.

It is concluded from these studies that:

(1) cold slows the speed of joint movement;

(2) joint stiffness results from local physical changes at the interarticular surfaces;

(3) the increased viscosity of synovial fluid resulting from a fall in temperature is a function of its mucin content;

(4) the characteristics of synovial fluid account for the increased forces required to move a cold joint and for the loss in speed of movement. *A. T. MacQueen.*

Variation in Serum Hyaluronidase-inhibitor during Treatment with 3-Hydroxy-2-phenyl-cinchoninic Acid (HPC). [In English.] FABER, V., and IVERSEN, M. (1952). *Acta med. scand.*, **143**, 436. 1 fig., 22 refs.

In this important paper the beneficial therapeutic effect of 3-hydroxy-2-phenylcinchoninic acid (HPC, "Oxinofen"), with relief of pain and joint swelling and a prompt fall of temperature, is confirmed in rheumatic fever, but not in rheumatoid arthritis. The authors, who were primarily interested in whether HPC had a corticotrophic action, found that the level of hyaluronidase inhibitor in the blood decreased concomitantly with clinical improvement as a result of treatment with HPC in five cases of rheumatic fever, but observed no comparable effect in the five cases of rheumatoid arthritis so treated at the Bispebjerg Hospital, Copenhagen. The drug had no effect on the 17-ketosteroid excretion or the eosinophil count. They were unable to demonstrate any effect of HPC on hyaluronidase or its inhibitor *in vitro*.

R. E. Tunbridge.

Electrophoretic and Chemical Study of the Serum Proteins in Rheumatoid Arthritis and their Modification under the Influence of Adrenal Cortical Therapy. (Étude électrophorétique et chimique des protides sériques au cours de la polyarthrite chronique évolutive et leur modification sous l'influence de la corticothérapie.) LAYANI, F., BENGUI, A., and MENDE, S. DE (1952). *Sem. Hôp. Paris*, **28**, 3221. 5 figs, 29 refs.

The authors studied the serum proteins and the effect on them of adrenocortical therapy in 25 cases of rheumatoid arthritis and eight healthy control subjects. Electrophoretic and chemical analysis of the serum proteins was made at least twice in each case, and the erythrocyte sedimentation rate was also determined.

Chemical analysis confirmed the existence of a general hyperproteinaemia, due to increase in the globulin content, on the one hand, and a depression of the albumin-globulin ratio, due to a concomitant reduction in the albumin content, on the other. Observations on healthy subjects revealed a similar tendency with increasing age, in the absence, however, of an absolute hyperproteinaemia.

Electrophoretic curves demonstrated that the greatest increase occurred in the α- and γ-globulin fractions. A striking parallelism was observed between the increase in erythrocyte sedimentation rate and that of the sum of β and γ fractions. In the γ fraction the greatest increase was recorded in the γ_1 subdivision, the portion of serum proteins usually regarded as the vehicle of antibodies.

The effects of ACTH therapy were studied in nine patients. An increase in serum albumin and a drop in α- and γ- globulin fractions were observed. The γ_1 subdivision was reduced but did not disappear under the influence of this hormonal treatment.

The authors point out the existence of wide discrepancies in the results of various investigators, and suggest that different techniques of electrophoresis may be responsible, as well as differences of opinion as to the range of normal values.

A. Swan.

17-Ketosteroid Excretion in Gout. BUTT, W. R., and MARSON, F. G. W. (1952). *Brit. med. J.*, **2**, 1023. 1 fig., 9 refs.

In a group of 33 patients with gouty arthritis, whose ages ranged from 36 to 70 years (mean 54·4 years), the daily urinary excretion of 17-ketosteroids measured by a polarographic method varied between 1·4 and 18·0 mg. (mean 9·5 mg.), the serum urate concentration varying from 4·8 to 12·7 mg. per 100 ml. (mean 7·7). The mean daily excretion of 17-ketosteroids in the four females in the group (mean age 66 years) was 5·0 mg. By the method used the daily excretion for normal males, aged 20 to 38 years, was 10 to 20 mg., and for normal females, aged 18 to 37, was 6 to 18 mg. When allowance was made for the fall in 17-ketosteroid excretion with age, all the results in the gouty patients, both male and female, were found to lie within the normal range.

M. Lubran.

Respiratory Effects of Salicylate. COCHRAN, J. B. (1952). *Brit. med. J.*, **2**, 964. 3 figs, 6 refs.

The effect of salicylate, given orally and by intravenous infusion, on oxygen consumption and output of carbon dioxide was studied in three patients with subacute rheumatism, one patient with quiescent rheumatoid arthritis, and five healthy young adults, three of the healthy subjects acting as controls. The Knipping spirometer, a modified Benedict-Roth spirometer which makes it possible to record both oxygen consumption and carbon dioxide output on the same record, was used.

Sodium salicylate was given intravenously over a period of 3 to 4 hours (10 g. in 400 ml. distilled water) to two healthy subjects and to the patient with rheumatoid arthritis, 10-minute spirometer tracings being taken at half-hourly intervals. The three patients with rheumatic fever received 1·5 to 2·0 g. aspirin by mouth five times a day after a satisfactory baseline had been reached as determined by three consecutive spirometer tracings taken each morning. Tracings continued to be taken after cessation of treatment until the spirometer records showed a return to pre-treatment levels.

It was found that the administration of salicylates produced an increase in depth of respiration and a marked increase in oxygen consumption. The fall in the respiratory quotient suggested that protein or fat was being mainly burned, but no conclusion could be drawn concerning the nature of metabolic stimulation. It was nevertheless considered that the increase in tissue oxidation following salicylate administration might be of fundamental significance in the therapeutic action of the drug. *A. T. MacQueen.*

Serological Studies in Rheumatoid Arthritis. II. Absorption of the Streptococcal Agglutinating Factor from Sera of Patients with Rheumatoid Arthritis by *Streptococcus haemolyticus* and *Staphylococcus aureus*. [In English.] OKER-BLOM, N. (1952). *Ann. Med. exp. Biol. fenn.*, **30**, 139. 8 refs.

Because of the agglutination of haemolytic streptococci by sera from patients with rheumatoid arthritis, *Streptococcus haemolyticus* has been regarded as a possible causal agent in this disease. *Staphylococcus aureus* also is agglutinated, however, and there are thus three possible explanations:

(1) the two organisms have a common antigen;

(2) serum from patients with rheumatoid arthritis has specific agglutinins against both organisms;

(3) the agglutination is a non-specific phenomenon.

This paper (the second of a series, the first of which was published by the author in 1948 (*Ann. Med. exp. Biol. fenn.*, 1948, **26**, 77)) is concerned with the first possibility listed above. Rabbits were immunized by intramuscular injections of heat-killed bacteria three times weekly for 4 weeks. They formed in response specific agglutinins which were absorbed only by the homologous antigen. Then from ten patients with rheumatoid arthritis samples of serum were obtained, each agglutinating staphylococci and streptococci to a titre between 1 in 80 and 1 in 640. Absorption with streptococci left no homologous agglutinins, but the staphylococcal agglutinins were not affected. Treatment with staphylococci absorbed both homologous and heterologous agglutinins. The author concludes on the basis of this and of the two (below) succeeding papers that agglutination in sera from patients with rheumatoid arthritis is a non-specific process. *E. G. L. Bywaters.*

III. Comparison between the Agglutination of *Streptococcus haemolyticus* and *Staphylococcus aureus* and Antistreptolysin and Antistaphylolysin Titers in Sera of Patients with Rheumatoid Arthritis. [In English.] OKER-BLOM, N., and WIDHOLM, O. (1952). *Ann. Med. exp. Biol. fenn.*, **30**, 144. 8 refs.

Here the possibility is examined that two different specific agglutinins co-exist in serum from rheumatoid arthritis patients. The relation between antistreptolysin O and antistaphylolysin and the agglutination titre for living *Streptococcus haemolyticus* and *Staphylococcus aureus* was examined, using sera from 48 cases of rheumatoid arthritis, and from 86 children aged 5 months to 10 years as controls. The sera were inactivated at 56° C. for 30 minutes and stored at —8° to —15° C. The authors mention the difficulties due to auto-agglutination. The results, which are clearly tabulated, show that there was no correlation between increased antistreptolysin-O titres and positive streptococcal agglutination tests, or between increased antistaphylolysin and agglutination titres in the sera from patients with rheumatoid arthritis. *E. G. L. Bywaters.*

IV. Absorption with Bentonite of the Streptococcal Agglutinating Factor from Sera of Patients with Rheumatoid Arthritis. [In English.] OKER-BLOM, N. (1952). *Ann. Med. exp. Biol. fenn.*, **30**, 150. 1 fig., 12 refs.

Here the results are reported of absorption of streptococcal agglutinins from the serum of rheumatoid arthritis by bentonite (colloidal aluminium silicate), a substance which is known to remove most of the lipids and some 70 per cent. of β-globulin from serum without causing any appreciable change in the other protein components of the serum. It was found that bentonite removed all trace of the rheumatoid-arthritis streptococcal-agglutinating factor, whereas parallel experiments with various types of antibacterial immune sera and with haemagglutinins showed only very slight absorption. It is concluded that the agglutination of living haemolytic streptococci by rheumatoid-arthritis sera is due to a non-specific factor probably occurring in the α- or β-globulin fractions, or both. *E. G. L. Bywaters.*

Determination of Iron in Blood Plasma or Serum. RAMSAY, W. N. M. (1953). *Biochem. J.*, **53**, 227. 1 fig., 25 refs.

The author describes a method for the determination of the iron content of serum or plasma which is of general application and depends on the replacement of the metal-combining globulin of the plasma by 2 : 2′-dipyridyl, which reacts with ferrous iron to give a highly-coloured ferrous-dipyridyl-complex ion. In practice, 2 ml. unhaemolysed plasma or serum is mixed with 5 ml. 0·5M acetate buffer solution (*p*H 5), containing 0·075 per cent. 2 : 2′-dipyridyl and 0·1 per cent. hydroxylamine hydrochloride and heated in a boiling-water bath for 5 minutes. The coagulated proteins are filtered off and the intensity

of the absorption band of the filtrate at 520 mμ measured in a spectrophotometer. The standard deviation of a single determination from the mean, calculated indirectly from seventy consecutive duplicate determinations, was ±5·1 μg. per 100 ml., or about 2·8 per cent. of the mean value. In 22 specimens from seventeen normal male subjects aged 19 to 44, the mean plasma iron concentration was 171 μg. per 100 ml. (S.D. 37) with a range of 112 to 225 μg. per 100 ml.; in three specimens from thirteen normal female subjects aged 19 to 24 the mean value was 127 μg. per 100 ml. (S.D. 29) and the range 78 to 170 μg. per 100 ml. These mean values are 30 to 60 μg. higher than those previously reported by other workers using other methods. The significance of these differences is discussed. *J. E. Page.*

Determination of Blood Serum Potassium by an Improved Sodium Cobaltinitrite Method. BARRY, J. M., and ROWLAND, S. J. (1953). *Biochem. J.*, **53**, 213. 1 fig., 10 refs.

The sources of error in the sodium cobaltinitrite method for the dete nination of potassium in blood serum have been invesiigated, and an improved analytical procedure developed. The low accuracy of earlier methods is attributed to the dilution of serum with water (which can lead to as much as 20 per cent. of the potassium remaining unprecipitated owing to the solubility of potassium sodium cobaltinitrite), to insufficient time being allowed for the precipitation of potassium, and to the loss of some of the precipitate during washing.

In the method described, the potassium is precipitated as potassium sodium cobaltinitrite by adding a sodium cobaltinitrite reagent to the serum in a centrifuge tube. After washing with aqueous ethyl alcohol the precipitate is dissolved in water and its cobalt content measured colorimetrically. It is claimed that the standard deviation of replicate determinations does not exceed 1 per cent. of their mean value, and that the recovery of added potassium is satisfactory. *J. E. Page.*

Plasma Cholinesterase Activity in Liver Disease: Its Value as a Diagnostic Test of Liver Function Compared with Flocculation Tests and Plasma Protein Determinations. WILSON, A., CALVERT, R. J., and GEOGHEGAN, H. (1952). *J. clin. Invest.*, **31**, 815. 1 fig., 27 refs.

At University College Hospital Medical School, London, the plasma cholinesterase activity was studied in 43 patients with liver and biliary-tract disease, in 44 convalescent patients with no evidence of liver disease, and in one hundred normal subjects, in order to determine its diagnostic and prognostic significance.

A well-marked depression of cholinesterase activity was observed in the group of 33 patients with liver disease. The mean value for normal subjects was 1,790 μl. CO_2 per ml. per hour (range 818 to 3,265 μl.), and in patients with liver disease it was 612 (range 238 to 1,086) μl. CO_2 per ml. per hour. This test was compared with flocculation tests, and it was shown that the depression of cholinesterase activity was a confirmatory finding in acute and subacute hepatic disease, and that it was a useful prognostic guide to recovery, since cholinesterase activity returns to normal more quickly than is shown by flocculation tests. In chronic liver disease, even when flocculation test results were normal, cholinesterase activity was usually depressed. Normal plasma cholinesterase levels were found on the ten patients with extrahepatic biliary obstruction of short duration, low values occurring during attacks of cholangio-hepatitis, or after prolonged obstruction. The test is less precise than flocculation tests in the differential diagnosis of jaundice, but in conjunction with these tests provides reliable information regarding impairment of liver function. *A. C. Frazer.*

Chemical Estimation of Cortisone-like Hormones in Urine. COPE, C. L., and HURLOCK, B. (1952). *Brit. med. J.*, **2**, 1020. 18 refs.

The authors point out the need for a simple quantitative test for the estimation of cortisone-like substances in body fluids, and they discuss the problems involved with reference to their own observations at the Post-graduate Medical School of London and to those of others reported in the literature.

The first step, the quantitative extraction of urine, can at present be carried out by two different methods:

(1) repeated extraction with chloroform after acid hydrolysis;

(2) Bayliss's method of triple extraction after hydrolysis with glucuronidase (*Biochem. J.*, 1952, **52**, 63).

The authors carried out parallel extractions by the two methods and assayed the extracts biologically by measuring the eosinopenia induced in adrenalectomized mice. The second method of extraction increased the yield by an average of 99 per cent. (range 8 per cent. to 315 per cent.) over that obtained by the first. The next step in need of simplification is the elimination of contaminants. The Porter-Silber reaction for the chemical assay of adrenal cortical hormone in the urine is the most sensitive available, but the result may be vitiated by the presence of certain contaminants which undergo the same colour changes as the hormones. The authors have therefore attempted to remove these contaminants by paper-chromatography and, so far as could be judged from biological assay, were able to recover all the hormone in a purified state. With extracts purified in this way the Porter-Silber reaction seemed to give a much more reliable index of the true adrenal hormonal content. Parallel assays were carried out, part of the yield of an extraction being assayed by the biological method and part by the chemical method after purification. In fourteen out of 23 assays the results given by the two methods agreed to within 30 per cent., the even scatter of the results suggesting that the differences were mainly due to experimental error. Biologically inert steroids present in the urine, of which tetrahydrocortisone is probably the most important, also give a yellow colour with the Porter-Silber reaction, but this will seriously affect the result only when they are present in abnormally high concentration. However, if absolute specificity in analysis is required, recourse must still be had to the biological method. *Ferdinand Hillman.*

Further Investigations into the Significance of Auto-antibody Estimations in Rheumatism and Organic Inflammatory Diseases. (Weitere entersuchungen zur Frage der klinischen Bedeutung von Auto-Anti-körpernachweisen beim Rheumatismus und bei entzündlichen Organerkrankungen.) VORLAENDER, K. O. (1952). *Z. ges. exp. Med.*, **120**, 9. 34 refs.

Fractional Estimation of 17-Ketosteroids in Rheumatoid Arthritis. (Über die draktionierte 17-Ketosteroid-bestimmung bei der Polyarthritis.) ENZINGER, J., and SCHMID, J. (1953). *Wien. Z. inn. Med.*, **34**, 28. 1 fig.

ACTH, Cortisone, and Other Steroids

Cortisone in Rheumatoid Arthritis. (Notre experience de la cortisone dans les rhumatismes chroniques inflammatoires.) MANTHA, L. (1952). *Un. méd. Can.*, **81**, 1156.

This article opens with an historical review of Cortisone treatment in rheumatoid arthritis from its discovery in 1949, and goes on to describe and discuss the author's personal experiences with this drug. He has treated 85 patients with cortisone in small doses—from 50 mg. daily to 25 mg. on alternate days, combined with gold injections and a theobromine-salicylate compound orally. (The dose of gold salt is given as 1/120 to 1/60 mg. weekly.) This treatment was continued for 12-15 months in twenty of these patients, but it did not appear to be more effective than the author's well-tried regime of gold therapy.

Treatment was stopped in the remaining 65 patients, mainly because of side-effects, of which fluid retention was the most common. In more than twenty cases, treatment was stopped at the patient's request.

[The incidence of side-effects seems high, in view of the rather small doses used. No indication is given in this article of the severity or activity of the disease in the cases treated; the fact that so many patients asked for treatment to be stopped suggests that some of these cases were in a relatively inactive phase.] *B. E. W. Mace.*

Combined Treatment with Cortisone and *para*-Amino-benzoic Acid [in Rheumatoid Arthritis]. (Kombinerad cortisone- och paraaminobenzoesyra-terapi.) OKA, M. (1952). *Nord. Med.*, **48**, 1407. 14 refs.

The effect of combined treatment with cortisone and *p*-aminosalicylic acid (PAS) was observed in twenty patients aged between 21 and 50 yrs who had suffered from rheumatoid arthritis for 6 mths to 18 yrs. Cortisone was given either intramuscularly or by mouth in a dose of 25 mg. daily, and the sodium PAS in doses of 1 to 1·5 g. at intervals of 2 to 3 hrs, to a daily total of 6 to 12 g. The average period of treatment was 36 days.

A favourable effect was noted in sixteen patients, with improvement of the general condition, an average gain of weight of 2·3 kg., and improvement in the condition of the joints. The four remaining patients showed improvement when the daily dose of cortisone was increased to 37·5 to 50 mg. Both routes of administration were equally effective. Treatment with cortisone or PAS was stopped in two groups of seven patients while treatment with the other compound was continued in either case; in both groups a deterioration of the condition of the joints appeared within a few days. The results indicate that suboptimal control over rheumatoid arthritis can be obtained with a dose of cortisone as small as 25 mg. per day when given combined with PAS. *D. J. Bauer.*

Trial of 3-Carboxylic Pyrocatechol in Rheumatic Fever, Rheumatoid Arthritis, and Certain Other Rheumatic Conditions. (Essai de pyrocatéchol 3-carboxylique dans le rhumatisme articulaire aigu, la polyarthrite chronique évolutive et certaines affections pararhumatismales.) MICHOTTE, L., and DANAUX, R. (1952). *Acta physiother. rheum. belg.*, **7**, 141. 6 refs.

Following up the idea that the active principle in salicylate therapy might be one of the accompanying impurities, the authors investigated the effect of 3-carboxylic pyrocatechol (a persulphuric oxidation product of salicylic acid) in twenty patients with acute rheumatic fever. The sodium salt of the drug was administered orally in doses of 0·5 g. 4-hrly. This resulted in a more rapid return to normal of the erythrocyte sedimentation rate, electrocardiographic appearances, and clinical condition than with salicylate or gentisate therapy, but the response was not so rapid as with cortisone. There was no marked effect in rheumatoid arthritis. One case of relapsed erythema nodosum responded satisfactorily, and a case of periarteritis nodosa with polyneuritis showed partial improvement. *I. Ansell.*

Resistance to Corticotrophin in the Treatment of Rheumatic Disorders. (Limites et échecs de l'ACTH en rhumatologie.) SÈZE, S. DE, RYCKEWAERT, A., ROBIN, J., and RENIER, J. C. (1952). *Rev. Rhum.*, **19**, 596. 2 figs, 12 refs.

The authors report nine cases of rheumatoid arthritis treated with ACTH. All the patients were adults and had active arthritis at the time of treatment; the duration of the disease varied from 5 mths to 15 yrs. The dosage of ACTH given was 75 to 100 mg. daily for 1 to 3 mths, and was then gradually reduced according to the condition of the patient. Results showed that in five cases there was a good initial response, with loss of pain, improvement of the joint condition, and a fall in the erythrocyte sedimentation rate. However, while still under treatment, all five cases relapsed between the fourth and seventh weeks and the disease progressed. In one case ACTH given intravenously was effective, but proved impracticable. All these cases responded favourably to subsequent treatment with cortisone. The other four cases never responded to ACTH, but responded adequately to cortisone. The reasons for the failure of ACTH therapy are discussed, and it is suggested that it was due to an abnormal adrenal response. *Kathleen M. Lawther.*

Cortisone, Corticotrophin, and Salicylates in the Treatment of Inflammatory Rheumatic Disease and Similar Conditions. (Cortisone, ACTH et salicylés dans le traitement des rhumatismes inflammatoires et des états similaires.) ROSKAM, J., and CAUWENBERGE, H. VAN (1952). *Presse méd.*, **60**, 1344. 4 figs, 25 refs.

The authors, writing from Liège, record their conviction that an endocrine mechanism is responsible for

the therapeutic effects of salicylates in rheumatic fever and the inflammatory rheumatic diseases; and that this mechanism consists of successive stimulation of the hypothalamus, anterior pituitary, and adrenal cortex. In experiments with rats they showed that heavy doses of salicylates evoke the same response as ACTH in respect to reduction of adrenal ascorbic acid and cholesterol, the circulating eosinophils, and nuclear changes in the cells of lymphoid tissue. By giving progressively decreasing doses of salicylates they further showed that the maximum reaction is obtained by that degree of salicylaemia found most efficacious in the treatment of rheumatic fever.

They then give case details of patients suffering from rheumatoid arthritis, chorea, rheumatic fever, and psoriasis, who developed a mild Cushing syndrome during treatment with aspirin in doses up to 8 g. daily, or during combined treatment with aspirin and a dose of cortisone considerably less (between one-quarter and one-half) than those usually considered effective. In cases responding unsatisfactorily to salicylate therapy it is claimed that the addition of these small doses of cortisone is beneficial.

The authors have devised a test which they suggest makes it possible to judge the probable efficacy of salicylate therapy in any case. Under controlled conditions blood and urine are collected 4, 6, and 8 hrs after the ingestion of 6 g. sodium salicylate. Patients showing a positive response will respond clinically to the administration of salicylates, a positive response being shown by a greatly increased ratio of uric acid to creatinine in the urine, up to 50 per cent. or more of its initial value after 4 hrs, and after 6 to 8 hrs a fall in the number of eosinophils to 50 per cent. of the initial value. *Kenneth Stone.*

Changes in Connective Tissue Reaction Induced by Cortisone. EBERT, R. H., and BARCLAY, W. R. (1952). *Ann. intern. Med.*, **37**, 506. 8 figs, 15 refs.

The authors, in experiments carried out at the University of Chicago, using their own modification of the Sandison rabbit-ear chamber, have demonstrated very clearly the soundness of some of the existing theories as to the action of cortisone upon the vascular system. The effect of cortisone was fundamentally the same in the normal preparations, in non-specific inflammatory reactions, and in tuberculous infections. Vascular tone was better maintained, there was less damage to the vascular system, and the amount of exudate and the leucocyte response were reduced. Their findings afford confirmation of the effect of cortisone on wound healing and of the possibility of a deleterious effect of cortisone on the condition of patients suffering from pulmonary tuberculosis. *R. E. Tunbridge.*

Effect of Cortisone upon Skin Sensitivity to Tuberculin in Sarcoidosis. PYKE, D. A., and SCADDING, J. G. (1952). *Brit. med. J.*, **2**, 1126. 10 refs.

The authors describe the effect of cortisone upon skin sensitivity in fourteen patients with sarcoidosis. Of the fourteen patients, eleven were negative to 100 tuberculin units (T.U.) of old tuberculin given intradermally, and ten of these received 100 mg. cortisone daily by intramuscular injection. In eight patients skin reactivity to tuberculin appeared 6 to 17 days after cortisone treatment was started, the reactions in six, with areas of induration, being maximum at 24 hrs and usually disappearing in 72 hrs. In two patients there were areas of erythema at 24 hrs, fading at 48 hrs. Later the reaction was less and faded more quickly. No reaction was observed in two patients at any time during cortisone administration. To nine patients normally Mantoux-negative an intradermal injection of 1·25 mg. cortisone was given with a dose of tuberculin equal to the highest dose to which they had previously failed to respond. An area of induration and erythema persisting at least 48 hrs was observed in seven, while there was no response in two. Similar injections of cortisone with tuberculin in three patients who were normally sensitive to 100 T.U. inhibited the reaction produced by tuberculin alone.

The authors suggest that the phenomenon they have observed in Mantoux-negative cases of sarcoidosis may prove to be of some practical importance as a diagnostic test. *I. Ansell.*

Effect of ACTH on Water Distribution in Man as Measured by Antipyrine, T 1824 and Bromide. ZIFF, M., SIMSON, J., and BUNIM, J. J. (1952). *J. clin. Invest.*, **31**, 829. 5 figs, 29 refs.

A study of the effect of corticotrophin (ACTH) administration on water distribution was carried out at New York University College of Medicine on five adult patients, of whom three had rheumatoid arthritis, one spondylitis, and one acute rheumatism. Determinations of antipyrine space, plasma volume (by the T 1824 dye method), bromide space, and total body chloride were made before, during, and after treatment with 100 to 120 mg. corticotrophin daily for about 4 weeks. Results are given in detail for each patient; in interpreting them, the antipyrine space is taken as representing total body water, and the bromide space extracellular fluid together with a portion of intracellular fluid. On administration of corticotrophin there was a marked increase in total body water in four cases, the increase in antipyrine space being confirmed by a gain in weight. In two of these four there was an almost parallel increase in bromide space and also in total body chloride, suggesting that the gain in body water was largely due to an expansion in the predominantly extracellular chloride compartment. In the other two patients the increase in bromide space and total body chloride was less than proportional to the gain in total body water implying that water retention in these cases was mainly intracellular, perhaps accompanying repair of atrophic muscle tissue. In the fifth patient an early increase in total body chloride and bromide space (without increase in total body water or body weight) appeared concurrently with signs of heart failure; later the total body chloride and bromide space diminished in spite of a rise in total body water. The plasma volume increased during treatment in three cases and fell in two; a protein shift, repair of anaemia, or a change in the permeability of the capillaries to T 1824 might have contributed to this finding.

It is clear that the amount and distribution of water retained in response to the administration of corticotrophin varies in different individuals, probably being determined, among other things, by the tissue requirements of the subject when treatment is started.

H. McC. Giles.

Inhibitory Effect of Cortisone on Strictures of the Urological Tract. BAKER, R., GOVAN, D., and HUFFER, J. (1952). *Surg. Gynec. Obstet.*, **95**, 446. 11 figs, 10 refs.

In experiments on dogs, cortisone was shown by the authors to depress the production of scar tissue about the ureter following uretero-sigmoidostomy, preventing the development of periureteric stricture and secondary hydronephrosis. This modifying influence of cortisone on fibroplasia was much less marked after re-anastomosis of the ureter to the uninfected bladder, little difference in the amount of scarring being observed between the cortisone-treated dog and the control animal.

On the basis of these observations the drug was used in combination with operative treatment in cases of urethral stricture and of total cystectomy with ureterocolostomy, a dose of 50 mg. being given intramuscularly twice daily for 2 days before and for about 3 weeks after operation. A convincing excretion pyelogram is reproduced, taken 8 months after total cystectomy for carcinoma of the bladder had been performed by the Coffey-I technique; very little dilatation is present and good "cupping" of the calyces is to be seen. In the treatment of urethral stricture the authors emphasize that excision, incision, or rupture of the stricture must be carried out if cortisone is to be of value. They issue a warning that the skin sutures should be retained for 3 weeks, the fascial planes should be sutured with steel wire, and the patient should be provided with an "antibiotic umbrella" during cortisone therapy.

K. Whittle Martin.

Corticotrophin and Cortisone in Management of the Nephrotic Syndrome in Children. RILEY, C. M. (1952). *J. Amer. med. Ass.*, **150**, 1288. 7 refs.

The effects on fifty patients with the nephrotic syndrome of treatment with corticotrophin or cortisone (parenterally or orally) or a combination of the two are reported. Only three of the patients were over the age of 16. Maximum daily doses in the older children (over 9 years) and in adults were 100 mg. corticotrophin and 300 mg. cortisone; in those cases in which a combination of the two drugs was given the daily dose of each was half of that given alone. A course of treatment lasted 10 days. No differentiation was made between cases of lipid nephrosis and cases of chronic glomerulonephritis in the nephrotic stage.

Only five of the patients failed to respond to this treatment at any time. The two drugs were about equally effective, but cortisone by mouth was the easier to administer. In some cases diuresis began during treatment, but more frequently it followed cessation of treatment. Diminished proteinuria and a rise in the serum protein level were not constant features of the diuresis. The duration of remission varied; in fourteen cases it was less than one month, while in some it lasted for as long as 2 years.

As regards methods of increasing the effectiveness of this treatment, the author had no success with sodium lactate or with small maintenance doses of cortisone, and the results with salt-poor human albumin were equivocal. The only death that appeared to be related to treatment occurred in a 3-year-old boy, death being due to acute renal failure following an infection, which was probably increased by the drug given. In all cases in which hypertension occurred blood pressure rapidly became normal on cessation of treatment.

It was impossible to forecast the outcome of treatment, because different results followed successive courses in the same patient. The author states that "no certain curative value can be claimed for these hormones at present".

K. G. Lowe.

Further Studies on the Treatment of Congenital Adrenal Hyperplasia with Cortisone. IV. Effect of Cortisone and Compound B in Infants with Disturbed Electrolyte Metabolism. CRIGLER, J. F., SILVERMAN, S. H., and WILKINS, L. (1952). *Pediatrics*, **10**, 397. 32 refs.

Metabolic studies were carried out on three infants with congenital adrenal hyperplasia at Johns Hopkins Hospital, Baltimore, in order to determine the most effective means of controlling the electrolyte and hormonal disturbance. It was established that cortisone was more effective than corticosterone (Compound B) in reducing the urinary output of 17-ketosteroids, whereas corticosterone was more effective in retaining sodium. Neither preparation, administered by itself, could adequately control both aspects of the disease except in doses which caused the development of "moon-face" and other toxic effects, but in two of the patients the combination of cortisone with a high salt intake proved satisfactory. In the third case deoxycortone acetate was also required. However, intercurrent infection or illness of any kind was liable to precipitate an Addisonian crisis and necessitated the administration of additional salt.

B. Nordin.

Effects of Adrenocortical Stimulation on Thyroid Function—Clinical Observations in Thyrotoxic Crisis and Hyperthyroidism. SZILAGYI, D. E., MCGRAW, A. B., and SMYTH, N. P. D. (1952). *Ann. Surg.*, **136**, 555. 15 figs, 50 refs.

A description is first given, from the Henry Ford Hospital, Detroit, of three cases of thyrotoxic crisis in which the administration of corticotrophin (ACTH) was followed by a rapid and considerable degree of improvement. Since, however, ACTH was not the only therapeutic agent used in these cases it was not certain that it was responsible for the observed improvement in the patients. An investigation was therefore made into the effect of ACTH in five other cases of hyperthyroidism, four of the patients having diffuse hyperplastic goitre and one a toxic nodular goitre. The effect of ACTH in these patients was estimated by measurement of the thyroid uptake and urinary excretion of radioactive iodine, the basal metabolic rate, and the serum protein-bound iodine and cholesterol levels.

The findings were by no means consistent, but it

seemed that thyroid function was significantly depressed in only one case and perhaps slightly in another, whereas it was augmented in a third case and in the remaining cases showed no significant change. All these patients, however, when operated upon had an exceptionally smooth post-operative course. The authors conclude with a discussion of the relationship of the pituitary-thyroid to the pituitary-adrenocortical axis, and it is suggested that the stress produced by thyroid over-activity can be minimized by simultaneously increased activity of the adrenal cortex. *G. A. Smart.*

Use of ACTH in Agranulocytosis. FULD, H. (1952). *Brit. med. J.*, **2**, 1133. 5 refs.

A case of agranulocytosis of unknown origin is described. The patient failed to respond to treatment, which included ACTH over a period of nine days. The prognosis for agranulocytosis of unknown aetiology remains grave in spite of the introduction of cortisone and ACTH.—[*Author's summary.*]

Effect of ACTH and Cortisone Therapy in Blood Disorders. DAVIDSON, L. S. P., GIRDWOOD, R. H., and SWAN, H. T. (1952). *Brit. med. J.*, **2**, 1059. 1 fig., 5 refs.

From the University of Edinburgh the authors report the results of ACTH and cortisone therapy in a series of 24 patients with various disorders of the blood. Of ten cases of thrombocytopenic purpura, six showed some response. In three of them there was clinical and haematological recovery, but since the illness in these cases had been of short duration the results were considered to be of doubtful significance. In the other three cases, which were of several years' duration, only temporary benefit was obtained. One of these patients, who had failed to respond to splenectomy 4 yrs previously, showed no response to 100 mg. ACTH daily for 10 days, but 8 mths later, on being given 800 mg. cortisone by mouth over 7 days, there was a temporary but substantial rise in the platelet count with a reduction in bleeding time. Another patient repeatedly responded to small courses of ACTH, but showed a higher platelet response to oral cortisone in the same dosage (100 mg. daily). In the last case there was a significant but temporary response to oral cortisone.

Four cases of non-thrombocytopenic purpura, apparently of the allergic type, failed to respond to hormone therapy.

Of two patients with idiopathic acquired haemolytic anaemia, one responded temporarily to ACTH, but not to oral cortisone. Splenectomy supplemented by ACTH was subsequently performed and resulted in delayed but eventual improvement. The other patient, who also had rheumatoid arthritis, obtained temporary benefit from both ACTH and cortisone therapy.

Hormone therapy was without benefit in aplastic anaemia (four cases), myelosclerosis (one case), acute leukaemia in adults (two cases), and eosinophilia and splenomegaly in infancy (one case). *L. J. Davis.*

Intravenous ACTH in the Treatment of Allergic Diseases. HAMPTON, S. F. (1952). *J. Allergy*, **23**, 493. 13 refs.

At Washington University Medical School, St. Louis, sixty patients, of whom 35 suffered from asthma and the rest from urticaria or dermatitis, received ACTH intravenously, as it had been reported that treatment by this route gave as good or even better results with considerably smaller doses.

Some were given daily infusions lasting 8 to 12 hours over a period of 2 to 10 days, the daily dose being 10 to 12·5 mg. in one litre of water and glucose.

Others received continuous intravenous infusions for 2 to 5 days, the concentration of ACTH in the infusate being the same.

A third group received daily infusions in the same way as the first group, but in addition one injection of 10 to 12·5 mg. ACTH was given intramuscularly at midnight.

The clinical results [details of which are not reported] were judged to be excellent. The fall in the eosinophil count and the increase in 17-ketosteroid excretion were pronounced. *H. Herxheimer.*

Effect of ACTH and Cortisone on the Rh_o Antibody Titre during Pregnancy. CHRISTENSEN, R. C., MARGULIS, R. R., and STEWART, H. L. (1952). *West. J. Surg. Obstet. Gynec.*, **60**, 429. 6 refs.

At the Henry Ford Hospital, Detroit, ten pregnant and two non-pregnant Rh-immunized women were treated with ACTH or cortisone to test the effect of these hormones on the process of isoimmunization; eight of the women had previously borne babies affected by haemolytic disease, whereas two had no previous history but were admitted to the trial on account of a rising anti-Rh titre. The two non-pregnant women presented residual titres from previous sensitization.

Each drug was first given intramuscularly; if no adrenal response was detected by the Thorn test 4 hrs later, it was given intravenously. (Cortisone was later also given orally.) The dose ranged from 75 to 100 mg. of either drug three to six times per week. When titres did not fall, intravenous ACTH was used (20 to 25 mg. in 300 ml. of 5 per cent. glucose in water). The shortest period of treatment was 3 days, and the longest 6½ months; the largest total doses given were 6,560 mg. cortisone and 300 mg. ACTH. The effects were judged according to fall of Rh titre and eosinophil count.

Spectacular falls in titre of anti-Rh_o (anti-D) were observed during treatment, the titre afterwards returning to normal. In six out of nine cases tested the Coombs' test showed no alteration as a result of treatment. The quickest response was found in the "albumin antibody titre", and one case is described in which the albumin titre fell from 1 in 1,024 to *nil*. In all patients the fall in titre was more than two dilutions, and therefore probably outside the limit of error. No ill-effects were observed; on the contrary, the patients tended to feel better and eat more, although in one patient pigmentation developed and another showed a general increase in hair. No infections were encountered. There were eight live births and two stillbirths; details of each case are shown in tables.

It is interesting to note that in the two non-pregnant cases the titre rose again to its previous level at the end of treatment. The observations are said to support the view that the Rh-antibody titre is not related to the degree of haemolytic disease in the child. The findings do not suggest that ACTH or cortisone has any beneficial effect upon erythroblastosis in the child; however, it was shown that prolonged treatment with these drugs apparently does little harm to the pregnant woman.

John Murray.

Experimental Study of the Psychological Changes Produced by Treatment with ACTH and Cortisone (Preliminary Results. (Étude expérimentale des modifications psychologiques produites par les traitements à l'ACTH et la cortisone (premiers résultats).) DELAY, J., PICHOT, P., PERSE, J., and AUBRY, J. L. (1952). *Encéphale*, **41**, 393. 4 figs.

In a series of eleven cases of chronic rheumatism an attempt was made to assess the psychological changes accompanying treatment with ACTH or cortisone. A test-retest method was used involving a non-verbal, culture-free intelligence test (Cattell, Forms 2A and 2B), a vocabulary (synonyms) test (Binois and Pichot), the F factor test (Cattell) and the Minnesota Multiphasic Personality Inventory (M.M.P.I.).

Contrary to the patients' subjective impression that intelligence improved with treatment, the results of the first two of the above-named tests indicated intellectual impairment. The resulks of the F factor tests were affected by the motor disturbances accompanying the disease and were therefore discarded. The results of the M.M.P.I. before treatment showed a slightly pathological personality such as is commonly found in cases of chronic illness, with a tendency to depression and hypochondriasis. After treatment the M.M.P.I. results revealed a general psychological improvement and amelioration in respect of depression, hypochondriasis, hysteria, and psychasthenia, but deterioration in respect of the K scale and of psychopathic deviation, paranoia, and hypomania, corresponding to increased euphoria and lowered moral values. Analysis of the individual M.M.P.I. scores showed that the treatment produced a general levelling out of scores in the direction of the patient's mean. The authors note the similarity between the changes they report and those observed with the same test in cases of leucotomy and in subjects under the influence of alcohol. *N. A. Standen.*

ACTH and Cortisone in Treatment of Complications of Leprosy. LOWE, J. (1952). *Brit. med. J.*, **2**, 746. 2 refs.

The treatment of leprosy with sulphone is now showing good results and the outlook is encouraging. The treatment of the complications of the disease, however, often presents serious problems. In this study 38 cases of leprosy showing complications were selected for treatment with corticotrophin (ACTH) or cortisone. The series was made up as follows: sulphone dermatitis (four cases); acute neuritis (eight); acute leprous eye inflammation (seven); lepromatous reaction (sixteen); tuberculoid reaction, leprous elephantiasis, and acute leprous arthritis (one case each). Corticotrophin was administered normally in doses of 25 mg. 6-hourly, and cortisone 100 mg. 12-hourly, the duration of treatment being 2 to 5 days; later, some of these doses had to be reduced because of adverse effects. Four cases of acute eye inflammation received cortisone eye drops.

The immediate results in the series were good, the acute conditions being readily controlled by hormone therapy. The most striking results were obtained in sulphone sensitivity, and in acute and subacute leprous eye inflammation, in which type of case hormone therapy is considered to be fully justified. In the other conditions, however, the underlying disease appeared to be aggravated by the treatment, and some bad late results were seen. Apart from cases of sulphone sensitivity and leprous inflammation of the eye, therefore, the author considers that hormone therapy of leprosy is usually contraindicated. *J. L. Markson.*

Cortisone in Ochronotic Arthritis. COPE, C. B., and KASSANDER, P. (1952). *J. Amer. med. Ass.*, **150**, 997. 4 figs, 10 refs.

A patient suffering from this disease which is characteristic of arthritis associated with pigment changes in skin, sclera, cartilage, and urine, showed marked temporary improvement when treated with cortisone. *P. L. Blaxter.*

ACTH and Cortisone in Ocular Trauma and in Eye Surgery: a Preliminary Report. THORPE, H. E. (1951). *Proc. Second Clin. ACTH Conference*, **2**, 340. 6 figs, 5 refs.

Eighteen cases of ocular injury and post-operative complications in eye surgery are reported, and the results of treatment with ACTH and cortisone are classified in six groups:

(1) effect on traumatic ocular inflammation (three cases);

(2) ACTH in traumatic eye surgery (six cases);

(3) effects of ACTH and cortisone on the healing and cicatrization of surgical incisions and drainage in glaucoma fistulating operations (three cases);

(4) effects of ACTH and cortisone on post-surgical oedema and inflammation in freshly operated acute congestive narrow angle glaucoma (two cases);

(5) beneficial effects of ACTH and cortisone in the course of a severe sympathetic ophthalmitis (one case);

(6) effects of hormonal treatment in two cases of traumatic cataract with "phaco-anaphylactic endophthalmitis".

The author describes in detail the intensive clinical, laboratory, and metabolic surveys undertaken in every case and the methods of giving the ACTH and cortisone. Side-effects are briefly discussed. The results of treatment and the conclusions which may be drawn from an admittedly short series of cases complete this paper.

The favourable effects of ACTH in post-traumatic inflammation, in the preparation of severely inflamed eyes with intra-ocular foreign bodies for surgery, in sympathetic ophthalmitis, and in severe post-operative reaction following acute glaucoma surgery are observed.

ACTH appears to have little effect on wound healing or scarring.

In the discussion, Scheie reported on the use of ACTH and cortisone following corneal grafting; Baxter gave an account of five cases in which wound healing before and during ACTH therapy were compared histologically; Gordon confirmed Thorpe's results in the treatment of sympathetic ophthalmitis and commented on the use of desoxycorticosterone acetate in eye disease. *J. R. Hudson.*

Local Use of Cortisone in Ophthalmology. (Applicazione locale di cortisone in oftalmologia (Risultati clinici).) CHINAGLIA, V., and FORONI, O. (1952). *Ann. Ottal.*, **78**, 535. 44 refs.

A review of the literature and report of the results obtained in 65 cases of ocular diseases treated by instillation or subconjunctival injection of cortisone. Dramatic results were obtained in vernal conjunctivitis, acute and subacute iritis and iridocyclitis, scleritis (particularly of rheumatic origin), phlyctenular kerato-conjunctivitis, and in some cases of keratitis, while retinal and choroidal exudative manifestations, glaucoma, neuritis, and diseases of the vitreous were not influenced.

N. Pagliarani.

Researches on the Permeability of the Blood-Aqueous Barrier. IX. Influence of the Local Administration of Cortisone. (Ricerche sulla permeabilita della barriera emato-oftalmica. IX. Influenza della somministrazione locale di cortisone.) SIMONELLI, M., and CALAMANDREI, G. (1952). *G. ital. Oftal.*, **5**, 364. 15 refs.

A decrease of the permeability of the blood-eye-barrier was demonstrated after the local administration of cortisone; this decrease was particularly evident in normal subjects under 15 years. This action is also marked in acute inflammatory conditions of the eye while in chronic cases it is delayed and less evident. The increase of the ocular permeability induced by subconjunctival injections of hyaluronidase is completely inhibited by cortisone. *N. Pagliarani.*

Ophthalmic Stress. (Doyne Memorial Lecture.) CAMPBELL, D. A. (1952). *Trans. ophthal. Soc. U.K.*, **72**, 457. 5 tables, 21 figs, 50 refs.

The ophthalmic conditions which may be considered as due to stress are migraine, glaucoma, miners' nystagmus, thyrotoxic exophthalmos, thyrotrophic exophthalmos, and myasthenia gravis. The physiological and endocrinological sequels of stress are considered and their application to ophthalmological conditions is demonstrated. The ophthalmological aspects of general diseases of stress are enumerated. Reference is made to the rise of blood sodium in the prodromal stage of migraine and to corresponding changes in water metabolism. The relationship of this to changes in the adrenal cortex and the pituitary gland is discussed. Changes in the blood sodium in cases of glaucoma are described and their influence upon the condition is suggested. Finally, the effects of sodium and water retention in cases of thyrotoxic and thyrotrophic exophthalmos are postulated and a plea is made for investigation of simple changes in the body, such as alterations of electrolytes. *A. G. Cross.*

Sarcoidosis treated with Cortisone. Report of a Case. DOLPHIN, A., and HEATHFIELD, K. W. G. (1952). *Lancet*, **2**, 1160. 1 table, 1 fig., 22 refs.

Case report with bilateral chorio-retinitis and secondary glaucoma treated by subconjunctival and parenteral cortisone: there was "little return of vision". Diagnosis was established by liver biopsy. *P. D. Trevor-Roper.*

Effects of Adrenocorticotropic Hormone (ACTH) and Cortisone on Sarcoidosis. SHULMAN, L. E., SCHOENRICH, E. H., and HARVEY, A. M. (1952). *Bull. Johns Hopk. Hosp.*, **91**, 371. 5 tables, 1 chart, 6 figs.

This is a survey of the results of treatment with ACTH and cortisone of fifteen cases of sarcoidosis; thirteen had ocular involvement.

It was noted that heightened adreno-cortical activity resulted in marked regression of signs of active sarcoidosis but that fibrotic changes were not influenced. Uveitis responded well, especially if it were of recent onset; there was a tendency towards relapse when the cortisone was discontinued, but the prolonged use of ophthalmic cortisone ointment kept two cases with anterior uveitis under control. If posterior uveitis were present, systemic administration was necessary.

Other ophthalmic manifestations such as conjunctival nodules were also suppressed by cortisone. *D. Ainslie.*

Temporal Arteritis and its Treatment with Cortisone and ACTH. WHITFIELD, A. G. W., COOKE, W. TREVOR, JAMESON-EVANS, P., and RUDD, C. (1953). *Lancet*, **1**, 408. 16 refs.

Twelve cases of temporal arteritis are reported in ten of which severe visual loss was featured in addition to pains of the head and neck. Intravenous drip administration of ACTH relieved the pain and pyrexia in all cases though the E.S.R. remained raised for a long period. It was also clear that this treatment should be continued for a long time lest relapse should occur, and in this series only two cases could, in fact, be treated until afebrile.

In five cases visual loss was of one or more week's duration before the start of treatment and was in no way benefited. In five others the duration was less than 10 days, and some recovery of vision was observed.

From the brief case histories recorded, it is not possible to deduce whether the visual loss was due to arterial or venous occlusion, though the record of papilloedema and profuse retinal haemorrhages in some cases suggests venous rather than arterial obstruction.

J. E. M. Ayoub.

Influence of Cortisone on Experimental Ocular Tuberculosis. (Influenza del cortisone sulla tubercolosi oculare sperimentale.) GRIGNOLO, A., and PANNARALE, M. R. (1952). *Rass. ital. Ottal.*, **21**, 242. 2 figs, 26 refs.

The action of cortisone, either local or general, was tested on two groups of guinea-pigs. The first group received for the first time a tuberculous inoculation into the anterior chamber, while the second group was composed of immuno-allergic animals which were re-inoculated intra-ocularly. In the first group, cortisone

caused an aggravation and acceleration of the course of the tuberculous infection; this was particularly evident after the local administration of cortisone (ophthalmic ointment). In the second group the course of the disease did not seem to be influenced by cortisone.

N. Pagliarani.

Influence of Cortisone on Swartzman's Phenomenon. [In Japanese.] MIZUKAWA, T., TAKAG,, Y., SUZUE, T., and KISHIMOTO, S. (1953). *Acta Soc. ophthal. Jap.*, **57**, 11.

As the first injection, diluted *B. coli* culture filtrate was injected into the vitreous of rabbits, and, as the second injection, a similar filtrate was given intravenously to cause Swartzman's phenomenon. When cortisone was given simultaneously with the first injection, the phenomenon appeared mildly. When it was given later, it was apt to have no effect.

It is interesting to note that a small amount of cortisone (5 mg.) impeded such reactions as an increase in protein of aqueous humour and an increase in the leucocyte blood count which appear after the first injection of the filtrate, whereas a higher dosage of cortisone (25 mg.) stimulated these reactions. *Y. Mitsui.*

Influence of Pituitary Posterior Hormone on the Intra-Ocular Distribution of Thiamine. [In Japanese.] TSUKAHARA, I. (1953). *Acta Soc. ophthal. Jap.*, **57**, 32.

In the previous report (*Amer. J. Ophthal.*, **35**, 886, 1952), the author stated that an intravenous injection of pituitrin alone did not result in an increase in the thiamine content of the retina and optic nerve. In this report he states that "atonin", a preparation of pituitary posterior hormone produced by the Dainihon-Zoki Co., can cause an increase of thiamine content in these tissues.

Y. Mitsui.

Influence of Pituitary Posterior Hormone on the Intra-Ocular Distribution of Thiamine. [In Japanese.] KISHIMOTO, M. (1953). *Acta Soc. ophthal. Jap.*, **57**, 36.

The author states that a combined intravenous injection of atonin and thiamine results in an increase in the thiamine content of the aqueous humour, while a combination of pituitrin and thiamine does not.

Y. Mitsui.

Effect of Intravenous Typhoid Vaccine on Adrenal Cortex Function. ROSEN, D. A. (1952). *Amer. J. Ophthal.*, **35**, 1783. 10 tables, 31 refs.

Fever therapy dates from about 1893. The pyrogenic factor common to all fever-producing agents is probably a polysaccharide so that the term "protein" shock is a misnomer. Many theories have been advanced as to the mode of action of these agents. The latest suggests that they cause an "alarm" or "stress" reaction and that their effect is due, at least in part, to activation of the adrenal cortex. Evidence supporting this concept is recorded by the author who found, in six patients receiving typhoid-paratyphoid vaccine for the treatment of various ophthalmic conditions, that among other changes produced there is an increase in the excretion of 17-ketosteroids and of 11-oxysteroids, and a decrease in the eosinophil count—effects similar to those induced by ACTH and cortisone.

A. Lister.

Synergistic Action of Cortisone and Total-Body Irradiation in Mice. WENTWORTH, J. H., and BILLOWS, J. A. (1952). *Radiology*, **59**, 559. 3 figs, 10 refs.

In a study, made at Brooklyn Hospital, New York, of the possible synergistic action between cortisone and whole-body irradiation, 48 male mice of the same inbred strain were given 750r of 220-kV *x* radiation. One group received, in addition, 1 mg. cortisone subcutaneously 12 hrs and 24 hrs before irradiation; a second group received 1 mg. cortisone daily after irradiation; a third group received irradiation only and served as controls; a fourth group received cortisone only. The animals receiving irradiation plus cortisone daily were all dead within 9 days, showing that the lethal effect of the combination was greater than that of either *x* rays or cortisone alone, although irradiation with 750r alone proved 100 per cent. lethal within 16 days.

The experiment was repeated with three groups of animals, 400r being given and the dose of cortisone being increased to two 3-mg. injections before irradiation. There were no deaths in the groups which received cortisone or irradiation alone, but of the group given cortisone plus irradiation nine were dead within 11 days and only four animals survived. The authors conclude that these results demonstrate the lethal synergistic effect of a combination of cortisone and irradiation. It is suggested that inhibition of the sulphydryl obligate intracellular enzyme system by inactivation of the sulphydryl radical is the common basic mechanism.

Margaret Ashton.

Miliary Tuberculosis in a Case of Acute Disseminated Lupus Erythematosus treated with ACTH. WALKER, B. (1952). *Brit. med. J.*, **2**, 1076. 17 refs.

Erythema Multiforme Exudativum. Report of a Case treated with Cortisone. WILLIS, W. D., and BARGAR, H. M. (1952). *Med. Bull. Europ. Command*, **9**, 160.

Other General Subjects

The So-called Diseases of Adaptation in Rheumatology. (Les maladies dites "de l'adaptation" en rhumatologie.) COSTE, F. (1953). *Sci. méd. prat.*, **28**, 5.

This is the text of an address delivered by Professor F. Coste at a conference organized in Paris by Dr. Albeaux Fernet. In it he examines the pros and cons of the adaptation theory as applied to the rheumatic diseases. Professor H. Selye, who attended the conference for the purpose, made a comprehensive and explanatory reply.

This interesting discussion cannot be abstracted adequately, but should be read in full by all who are interested in this aspect of disease. *W. S. C. Copeman.*

Rheumatic Disorders of the Liver. (Über rheumatische Hepatopathien.) SCHMENGLER, F. E. (1952). *Medizinische*, **49**, 1553.

The author first noted the association of hepatic damage with rheumatism in 1938 when, in cases of acute articular rheumatism (without jaundice) it was found that a number of common liver function tests gave consistently abnormal results. He now reports the results of studies carried out at the Düsseldorf Academy on the liver changes in chronic rheumatism, which were investigated clinically and by means of liver function tests and the examination of liver tissue obtained by biopsy; blind punch biopsy is, in the author's opinion, both dangerous and unreliable, and peritoneoscopy was consequently employed for this purpose. A series of thirty patients with active or latent forms of chronic articular rheumatism were examined, one at necropsy. In 21 cases enlargement of the liver was obvious, its edge being sometimes felt a hand's breadth below the costal margin. In 21 cases again [though not necessarily the same 21] the erythrocyte sedimentation rate was markedly accelerated; the Takata reaction, carried out in twenty cases, was positive in fifteen, and the thymol turbidity test gave a positive result in most cases. Electrophoretic studies of the serum proteins were performed in 23 cases and showed an increase in the γ-globulin component in sixteen, and in the β-globulin component in six. The combination of increases in β- and γ-globulin is assumed to be characteristic of liver damage. The macroscopic and microscopic appearances of the affected livers are fully described, as well as the stages leading to chronic hepatitis and, ultimately, to the fully developed syndrome of rheumatic cirrhosis of the liver. *D. Preiskel.*

The Rheumatic Neurosis. (La nevrosi reumatica.) ANTONELLI, F. (1952). *Policlinico prat.*, **59**, 1669.

The "rheumatic neurosis" is a psychosomatic syndrome presenting symptoms of a rheumatic type and occurring in individuals whose personality shows certain characteristic traits. It is aggravated by psychic trauma. Anatomical and pathological changes are either absent or negligible, but the development of the rheumatic neurosis is often followed by the establishment of clear-cut rheumatoid arthritis, or may be a sequel of that disease. The author distinguishes four types:

(1) pure, (2) superimposed, (3) residual, (4) somatopsychic (chronic arthritis with a secondary reactive personality disorder).

In a series of approximately 1,000 patients attending the Rome Rheumatological Centre, 20 per cent. showed the pure form of the neurosis. Since women predominated in this series, the author confined his personality studies to the female patient. He concludes that women suffering from rheumatic neurosis are characteristically hyperactive and domineering, are rigid disciplinarians, sexually frigid, and hostile towards the male sex. Their mothers show the same character traits. In his opinion these personality features are the result of repressed aggression, which is also responsible for the muscular tension and pain from which these patients suffer. Treatment consists in individual and group psychotherapy, re-education of the patient, occupational therapy, and sedation.

P. Carsar.

Polyneuritis after Treatment with Isoniazid. (Polyneuritis nach Isonikotinsäurehydrazid.) MOHNKE, W., and SCHRÖDER, R. (1952). *Med. Klinik*,, **47**, 1594. 5 refs.

The authors report from the Municipal Hospital, Bielefeld, eleven cases of disturbance of the peripheral nervous system, in three instances progressing to a true polyneuritis, which developed during the treatment of one hundred tuberculous patients with isoniazid. A dosage of 0·2 g. of the drug four times daily (5 to 15 mg. per kg. body weight) was employed, as this dosage was found necessary to maintain a bacteriostatic concentration in the blood stream. In addition to the symptoms mentioned, some patients also suffered from headache, faintness, and allergic exanthemata. After a total dose ranging from 4 to 28 g. had been given, paraesthesia appeared in the hands or feet, followed in some cases by the loss of reflexes, hyperalgesia, hyperidrosis, and trophic disturbances. Paraesthesia later spread to the lower leg and forearm. If treatment was continued, walking became very painful, there was severe pain when pressure was applied over nerves, urination became very difficult, and bladder sensation was lost.

The only cases to develop polyneuritis were those in whom, in accordance with the advice of previous workers, treatment had been continued after warning signs of paraesthesia had occurred. In other cases the therapy was interrupted for 8 to 21 days, after which it was found that the drug could again be given without ill-effect. The changes found were typical of the toxic neuritis found after the administration of sulphonamides, lead, and other drugs. The question whether the symptoms were due to the isoniazid or to toxins released from the bacteria is discussed; in favour of the latter explanation was the advanced state of the disease. It is noteworthy that all the cases of paraesthesia developed in the 50 per cent. of chronic patients who had received previous treatment with "conteben" (thiacetazone).

Robert Hodgkinson.